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Recent advances in the engineering of nanosized active pharmaceutical ingredients: promises and challenges

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Abbreviations

AFR, aerosol flow reactor; API, active pharmaceutical ingredient; ASES, aerosol solvent extraction system; AUC, area under the blood concentration; BSA, bovine serum albumin; CQA, critical quality attributes; C_{max}, maximum plasma concentration; CSD, colloidal silicon dioxide; DCP, dibasic calcium phosphate anhydrous; DMA, dimethylacetamide; DPI, dry powder inhalers; DSC, differential scanning calorimetry; EPAS, evaporative precipitation into aqueous solution; Eq, equation; GAS, gas anti-solvent; HGAP, high gravity antisolvent precipitation; HGCP, high gravity controlled precipitation; HGRP, high gravity reactive precipitation; HIV, human immunodeficiency virus; HP-β-CD, 2-Hydroxypropyl-β-cyclodextrin; IV, intravenous; HPC, hydroxypropyl cellulose; HPH, high-pressure homogenization; ILC, inulin lauryl carbamate; IVIVC, in vitro in vivo correlation; MCC, microcrystalline cellulose; NSAID, nonsteroidal antiinflammatory drug; P-gp, P-glycoproteins; PLGA, poly(lactide-co-glycolide); PLM, polarized light microscope; PSD, particle size distribution; PVA, polyvinyl alcohol; PVP, polyvinylpyrrolidone; RPB, rotating packed bed; RESS, rapid expansion in supercritical fluid; SAS, supercritical anti-solvent; SCF, supercritical fluid; SLNs, solid lipid nanoparticles; SDS, sodium dodecyl sulphate; SEDS, solution-enhanced dispersion by supercritical fluids; SDC, sodium deoxycholate; SEM, scanning electron microscopy; SFL, spray freezing into liquid; SGF, simulated gastric fluid; SLS, sodium lauryl sulphate; TEM, transmission electron microscopy; TPGS, D–α–tocopherol polyethylene glycol succinate; TPP, tripolyphosphate; UWL, unstirred water layer; WGG, wheat germ agglutinin; XRPD, X–ray powder diffraction.

Contents

Abstract

The advances in the field of nanotechnology have revolutionized the field of delivery of poorly soluble active pharmaceutical ingredients (APIs). Nanosized formulations have been extensively investigated to achieve a rapid dissolution and therefore pharmacokinetic properties similar to those observed in solutions. The present review outlines the recent advances, promises and challenges of the engineering nanosized APIs. The principles, merits, demerits and applications of the current 'bottom-up' and 'top-down' technologies by which the state of the art nanosized APIs can be produced were described. Although the number of research reports on the nanoparticle engineering topic has been growing in the last decade, the challenge is to take numerous research outcomes and convert them into strategies for the development of marketable products.

Keywords: Bioavailability; Dissolution rate; Nanoparticle engineering; Nanosizing; Poorly soluble APIs; Solubility.

1. Introduction

Nanoparticles refer to solid colloidal three-dimensional particles in the size range from 1 to 1000 nm [1]. Therapeutically, nanoparticles could be used as API carriers (vehicles) through dissolving, entrapping or adsorbing the API. Historically, nanoparticles have been developed for API delivery since the 1960s [2]. Commercially, the first approved product employing nanoparticle formulation was **ABI-007 (Abraxane®; American BioScience Inc., Santa Monica, CA)** [3]. Nanotechnologies have been employed for the treatment of several diseases such as cancer [4], tuberculosis [5,6], etc. Nanotechnologies have been used to improve the solubility of hydrophobic APIs by two main approaches. The first approach involves the production of nanocrystals using techniques based on down-up methods, top-down methods, or a combination of top-down and down-up methods. The second approach involves nanotechnology-based API delivery dosage forms such as polymeric micelles, nanosuspensions and/or nanoemulsions [7].

2. Solubility of nanosized APIs

APIs administered orally have to be in the solution state to be absorbed and consequently induce a therapeutic response. It is estimated that at least 40% of the newly identified APIs are low soluble materials [8], making the formulation of such compounds challenging in the pharmaceutical industry. Therefore, universal solubilization methods that can significantly improve the APIs' bioavailability are still highly desirable. In the literature, many techniques were used to improve the solubility of poorly soluble APIs, such as complexing APIs with cyclodextrins [9], conjugation to dendrimers [10], salt formation of ionizable APIs [11], solid dispersions [12], and lipid-based API delivery systems such as microemulsions and liposomes [13]. Nevertheless, some of these techniques were unsuccessful and thus the molecules were abandoned during early stages of development, or the product being launched exhibited suboptimal properties, including the poor bioavailability, the lack of fed/fasted equivalence, the lack of optimal dosing and the presence of extra excipients that pose limitations with respect to dose escalation, and ultimately a poor patient compliance [14].

Nanosized APIs proved promising properties in all stages of the API development process. According to the Nernst–Brunner/Noyes–Whitney equation [15–17], increasing the saturation solubility of an API will increase its dissolution rate from the pharmaceutical dosage form. This is described in equation 1 (Eq. 1; [18]).

$$\frac{dX}{dt} = \frac{A.D}{h}\left(Cs - \frac{Xd}{V}\right) \quad \textbf{(Eq. 1)},$$

where dX/dt is the dissolution rate, Xd is the amount dissolved, *A* is the particle surface area, *D* is the diffusion coefficient, *V* is the volume of fluid available for dissolution, *Cs* is the saturation solubility and *h* is the thickness of the effective boundary layer. Based on the above equation, the decrease of particle size will increase the effective particle surface area (*A*), eventually leading to an enhanced dissolution rate and thus an increased **API bioavailability** [19]. The applicability of this theory has been verified by many researchers [20,21]. Additionally, according to the Prandtl equation (Eq. 2), the decrease in particle size achieved for nanosized APIs will lead to a decrease in the thickness of the effective boundary layer, ultimately resulting in an increased API dissolution rate [22].

$$hH = k\left(\frac{\sqrt{L}}{\sqrt{V}}\right) \qquad \textbf{(Eq. 2)},$$

where *L* is the length of the surface in the direction of flow, *k* is a constant, *V* is the relative velocity of the flowing liquid against a flat surface and *hH* is the thickness of the hydrodynamic boundary layer.

Additionally to the enhanced dissolution rate explained above, nanosized APIs have increased saturation solubility compared to an unmilled product of the same API, as illustrated by Freundlich–Ostwald equation [23,24] (Eq. 3).

$$Cs = C\infty\, e^{\left(\frac{2\gamma M}{rpRT}\right)} \qquad \textbf{(Eq. 3)},$$

where *Cs* is the saturation solubility of the nanosized API, *C*∞ is the saturation solubility of an infinitely large API crystal, γ is the crystal-medium interfacial tension, *M* is the compound's molecular weight, *r* is particle radius, ρ is density, *R* is a gas constant and *T* is the temperature.

Based on the above equation, C_s is a function of the interfacial tension (γ) and therefore is a function of the interfacial energy *G* ($G = \sigma \cdot A$). High energy surfaces are likely to be created on

the surface of the milled nanosized API particles compared to parent microsized particles. Such differences in the interfacial energy may contribute to differences in C_s between nanosized and microsized APIs [25]. For example, Ganta *et al.* [26] showed how the saturation solubility of Asulacrine has dramatically increased for milled preparations compared to un-milled preparations. The solubility increased with successive size-reduction steps and the highest solubility was achieved with a median particle size of 133 nm.

3. Bioavailability of nanosized APIs

The number of poorly water-soluble APIs is increasing and, therefore, new methods to enhance their dissolution rates are always warranted [27]. Nanosized API particles received much interested due to their high specific surface areas and, therefore, their marked enhanced dissolution rates and bioavailabilities [25,28–35]. Most nanosized API formulations contain a stabilizer (usually a surfactant), which is likely to increase the wettability of hydrophobic APIs leading to an increased dissolution rate [36].

In the literature, the efficiency of the oral delivery of poorly soluble APIs was improved using several nano-strategies such as nanosuspensions [37], nanoemulsions [38], nanocrystals [39], polymeric nanoparticles [40], solid lipid nanoparticles (SLNs) [41], nanosized APIs loaded in mesoporous matrices[42,43], etc. Stable amorphous nanoparticle APIs with enhanced bioavailability have also been prepared [44]. The advantages of mesoporous nanomatrix formulations over polymeric nanoparticles include the ordered nanoscale porosity, the opportunity to control the size and morphology, the high specific area, the good stability and the high API loading capacity [45–47].

APIs usually get absorbed maximally at the duodenal-jejunal area, thus if the dissolution of an API was not completed in this area then the bioavailability of this API will be seriously compromised. In contrast to large API particles, which cannot adequately be dissolved in a specific absorption window, nanosized API particles are rapidly dissolved during the transit through the gut, potentially leading to a maximal absorption and an improved bioavailability [48].

It has also been hypothesized that the increased bioavailability of the nanosized APIs compared to the unmilled APIs could be attributed to the increased effective intestinal permeability (by

diffusion through the epithelial cell membrane) for nanosized APIs, attributable to the decrease in the thickness of the unstirred water layer (UWL, a layer of water that is adjacent to the mucous membrane of the intestinal wall), ultimately leading to an increased amount of API that reaches the systemic circulation [49].

Recently, there have been increased attention towards both biorelevant *in vitro* [50] and *in silico* [36] methods for predicting the performance of nanosuspensions.

For example, Juenemann et al [50] evaluated the ability of *in vitro* biorelevant dissolution methods to predict the *in vivo* performance of both nanosized fenofibrate and microsized fenofibrate. A good correlation was demonstrated between the predicted *in vivo* performance and the biorelevant *vitro* dissolution method under the assumption that there is a permeability restriction. **Simulated profiles showed the rate-determining step for absorption to change from dissolution-controlled in the case of micronized formulations to at least partly permeability-limited in the case of nanosized formulations. Gastric emptying was however shown to be a rate-determining for the absorption of fenofibrate from both the microsized and the nanosized formulations.**

When developing a dissolution method for nanosuspensions, the redispersibility analysis of the simulated gastric fluid (SGF) should be conducted to provide an initial estimate of the potential bioperformance. Particle size distributions should be measured before and after the redispersibility. Care should be considered to ensure the separation between the dissolved and undissolved material [36]. Jinno *et al.* [51] used a mixing tank model to predict the dissolution rates of cilostazol suspensions prepared using different techniques (hammer-mill, jet-mill and the nanocrystal technology). Good correlations were established showing that the dissolution rate of cilostazol was increased with the reduction in particle size. Shono *et al*. [36] confirmed that the bioavailability of nanosuspensions is guided by several factors, i.e., the increase in dissolution rate, the increase in saturation solubility and the reduction in effective permeability. However, it should be kept in mind that taking all the foregoing factors into account simultaneously could be complicated.

4. Nanosized APIs in oral delivery systems

Nanosuspensions can be processed into dry powder and subsequently shaped into solid oral dosage forms such as capsules and/or tablets. Two approaches are currently available to achieve this goal [52]. The first approach is a two-step process. Nanosuspensions are subjected to solvent removal. Then, the resultant powder is further mixed with a suitable excipient before tableting or capsule filling. For example, rutin nanocrystals were freeze-dried and then incorporated into tablets that have shown improved API dissolution rate in comparison to the marketed product [53]. The second approach involves the formation of granules by using the nanosuspension solvent as a granulation liquid or layering dispersion in the fluidized bed process. However, such formulations may exhibit irreversible aggregation that is likely to lead to decreased bioavailability. A dispersant is usually used to prevent such aggregation. A study by Rao *et al* [54] found that sugars alone (25–250 %, w/w) were not effective to prevent aggregation of albendazole nanosuspensions. However, such aggregation was no longer observed when 12.5 % (w/w) hypromellose, or 2.5 % (w/w) carbopol, were additionally used.

Many solvent removal techniques have been employed to solidify nanosuspensions, including freeze-drying, spray-drying, vacuum-drying, oven-drying and fluidized bed-drying, as summarized in Table 1.

Table 1. A summary of some drying techniques used to isolate nanosized APIs from nanosuspensions (the grades used of MCC, DCP, silica and ILC were Avicel® PH101, Fujicalin®, Aerosil®200 and Inutec®SP1 respectively) (*the stabilizer prevents the nanoparticle aggregation within a colloidal dispersion before drying; **the matrix former prevents nanoparticle aggregation within a solid phase following drying).

Drying technique	API	Nanosizing method	Stabilizer*	Matrix former**	Reference
Freeze-drying	Rutin	HPH	SDS or Tween 80	…	[53]
	Azithromycin	HPH	Pluronic F68, tween 80 and lecithin	…	[55]
	Oridonin	HPH	Pluronic F68 and lecithin	Mannitol	[56]
	Ascorbyl palmitate	HPH	Tween 80	Trehalose	[57]
	Danazol	Media milling	Mannitol	PVP	[58]
	Iitraconazole	Media milling	TPGS	MCC	[59]
	Naproxen	Media milling	HPC and arginine	None	[60]
	Cinnarizine, griseofulvin, indomethacin, itraconazole, loviride, mebendazole, naproxen, phenylbutazone and phenytoin.	Media milling	TPGS	MCC	[61]
	Lovastatin	Sonoprecipitation	PVP/Pluronic F68/hypromellose and SDC	Mannitol and glucose	[62]
Spray-drying	Itraconazole	Microprecipitation-HPH	Poloxamer 188 and SDC	Mannitol	[63]
	Fenofibrate	Antisolvent precipitation	SDS and hypromellose E3	Lactose and Mannitol	[64]
	Celecoxib	Emulsion-diffusion	PVP or SDS	…	[65]
	Cinnarizine, griseofulvin, indomethacin, itraconazole, loviride, mebendazole, naproxen, phenylbutazone and phenytoin.	Media milling	TPGS	MCC, DCP, silica or ILC	[66]
	Salbutamol sulphate	HGCP	…	…	[67]
Vacuum-	Itraconazole, sofalcone, fenofibrate,	Media milling	HPC	Carrageenan and alginic	[68]

drying	cilostazol and naproxen.			acid and gelatine	
	Artemisinin	Evaporative precipitation	…	…	[69]
	Quercetin	Evaporative precipitation or HPH	Pluronic F68 and lecithin	…	[70]
	Cefixime	Sonoprecipitation	PVP	…	[71]
	Indomethacin	Ink jetting nanosuspension	L–arginine and PVP	…	[72]
Oven-drying	Griseofulvin	Media milling	HPC and SDS	*α*–lactose–monohydrate	[73]
	Ketoconazole	Medial milling	Hypromellose, poloxamer, PVP and SLS	*α*–lactose–monohydrate	[74]
Fluidized bed processing	Naproxen	Media milling	TPGS and hypromellose	Sucrose and corn starch	[75]
	Cinnarizine	Media milling	TPGS and hypromellose	Sucrose and corn starch	[75]
	Azodicarbonamide	Media milling	SDS	*α*–lactose–monohydrate	[76]

Freeze-drying has been applied immediately after mixing of an API dissolved in an organic solvent with an antisolvent solution [77]. Controlled crystallization during freeze-drying was employed to control the size of the nano-freeze-dried fenofibrate [78]. Badawi *et al*. [79] freeze-dried a nanosuspension of itraconazole (a class II API) to prepare a solid dosage form. However, the produced itraconazole nanocrystals exhibited a high degree of aggregation and consequently a decreased dissolution rate. Such aggregation was reduced by using a dispersing agent containing Avicel PH 101® and Aerosil 200®. More examples from the literature include the use of freeze-drying to isolate albendazole [54], azithromycin [55], danazol [58], itraconazole [59], naproxen [60], oridonin [56], griseofulvin, indomethacin, loviride, mebendazole, naproxen, phenytoin [61], cinnarizine and phenylbutazone [66] nanosized particles.

Spray-drying has been increasingly used as a drying procedure of nanosuspensions produced by either bottom-up or top-down methods. For example, nanosized nifedipine prepared by high-pressure homogenization (HPH) were spray-dried to isolate a solid product. Naproxen nanosuspensions produced using media milling technology were converted into dry powder nanocrystals using vacuum-drying. Other examples include the use of vacuum-drying to isolate the solid product of itraconazole, sofalcone, fenofibrate, cilostazol, naproxen [68], artemisinin [69] and quercetin [70]. Oven-drying was used to isolate many nanosized API crystals such as CRS 74 (a new antiretroviral drug) [80], indomethacin [72], lovastatin [62] and cefixime [71]. Additionally, fluidized bed process was used to dry several nanosized APIs such as griseofulvin [73], ketoconazole [74], naproxen, cinnarizine [75] and azodicarbonamide [76]. Ibuprofen nanocrystals produced by melt emulsification were dried using fluidized bed process [34].

Regardless of the drying method applied, nanosuspensions could aggregate upon drying, leading to a decreased API bioavailability obtained from solid dosage forms [81]. For example, a decreased bioavailability was observed for Danazol® capsules compared to a liquid nanosuspension preparation [82]. Spray-dried nanocrystals usually show a high degree of aggregation when processed into tablets, such aggregation was prohibited when itraconazole nanocrystals were dispersed using mannitol and sodium deoxycholate (SDC) [63]. Vacuum dried naproxen nanocrystals also exhibited a high degree of aggregation, such aggregation was presented using carrageenan, gelatin and alginic acid used at concentrations above 12.5%, 50%

and 25% respectively [68]. Oven dried itraconazole nanocrystals showed little aggregation and up to 60.4% dissolution rate after 10 min [68]. In general, the aggregation induced by drying may be avoided by using carefully selected excipient such as sodium lauryl sulphate (SLS), sodium docusate and rapidly hydrating agents (e.g., carbohydrate based excipients) [41].

Formulating nanosized APIs into an oral dosage form possesses many advantages. For example, utilizing a nanosized API in oral dosage forms will have an effect on the P-glycoproteins (P-gp). Many studies referred that the use of a stabilizer in nanosized formulations inhibits P-gp that is located in the apical membrane of the intestine [83]. However, all studies used *in-situ* methods such as the cacao cell culture everted gut sac and single pass perfusion with no *in vitro in vivo* correlation (IVIVC) been established [52].

Hydrophobic APIs usually show significant variations in the absorption between the fed and fast states. The API dissolution might be enhanced in the fed state due to many factors such as the delayed gastric emptying, increased gastric pH, increased gastric volume, increased bile secretion and increased splanchnic blood flow. Nanosized delivery systems have also the merit of minimizing the fed/fast fluctuations observed with some formulations intended for oral drug delivery [84]. For example, commercial megestrol acetate formulation showed significant fluctuations in the maximum plasma concentration (C_{max}) and area under the blood concentration–time curve (AUC) in the fed state as compared to fast-state; however, the nanosized formulations showed reduced fluctuations and improved oral bioavailabilities compared to the commercial formulation [85]. Similar findings were reported for fenofibrate, a traditional example of a hydrophobic API that shows variations in the absorption between fed and fasted states. The extent of absorption varies from 30% to 50% and from 60 to 90% in the fast-state and the fed state respectively. However, the administration of nanosized fenofibrate has led to the absence of food effect (i.e., fed/fasted state variations) in human [32].

Nanoparticles have a unique ability of adhesiveness to the biological barrier, such characteristic can be further enhanced by adding special excipients in the formulation such as mucoadhesive polymers (e.g., carbopol and chitosan) [86].

Compared to suspensions of microsized APIs, suspensions of nanosized API formulations have been shown to achieve higher levels of systemic exposure (the amount of drug that exerts biological action) to *in vivo* dissolution media, due to their higher surface areas and

higher dissolution rates [30]. Such increase is an important step at the preclinical studies because it can lead to a considerable reduction in the amount of API needed for toxicological studies [41]. Nanosized APIs could **also be** used in controlled release dosage forms. For example, ketoprofen controlled release pellets were studied to combine nanosuspensions produced by the nanocrystal technology with modified release technology [87].

5. Nanosized APIs in pulmonary delivery systems

Nanoparticles are attractive for API delivery to the lungs and, therefore, they have become a subject of a very active research. This is because aerosol formulations containing nanosized APIs have many advantages over traditional aerosol formulations [88–91].

Nanosized APIs can be suitable for the delivery to the deep lung because of their low-density microstructure. Applying nanotechnology to particle engineering to enhance pulmonary drug delivery is one of the most attractive advances [92]. Engineering nanosized formulations offers the opportunity to control the physicochemical properties of the resultant formulations, i.e., producing nanoparticles with predetermined properties [93]. For example, nanosized APIs have been engineered in terms of size and shape to avoid the clearance and increase the residence time at the site of action [3]. Nanoparticles could be agglomerated in a controlled manner to achieve micro-sized particles with both improved aerosolization and dissolution behaviors [94]. For instance, micron-sized structures composed of polystyrene, polyacrylate, gelatin or chitosan were engineered from nanoparticles to enhance the delivery efficacy of APIs to the lung [91,95–98]. Large porous agglomerates with a large geometric diameter but a small aerodynamic diameter were also engineered from nanoparticle drug formulations [99–101]. Inhaled nanoparticles formulated with polysorbate 80 and poloxamer 407 containing itraconazole proved a better physiological efficiency and a reduced required effective dose in comparison to the oral delivery [102]. Nanosized API particles were used to coat microsized API particles and thus a reduced degree of API-API cohesive forces was achieved [103,104]. Polymeric nanoparticles proved to be potential for pulmonary drug delivery [105]. Nanoparticles have a higher likelihood of biotransfer into the blood through the pulmonary membrane and, therefore, they may be potential for intracellular drug delivery [93].

Drug release from nanoparticles can be altered by manipulating their biodegradation process [106]. Therefore, nanoparticles may be advantageous to provide sustained release (i.e., increasing the residence time of APIs in the airways), which offers dose frequency reduction and better patient compliance [107,108]. Generally, a sustained release of an API to the lung could be obtained via the use of mucoadhesive materials such as chitosan, a biodegradable poly-saccharide. For instance, preparing chitosan surface-modified poly(lactide-co-glycolide) (PLGA) nanoparticles resulted in a prolonged release of elcatonin (a protein API) and consequently a prolonged reduction in blood calcium levels compared to unmodified PLGA nanoparticles [109].

Sodium alginate formulated with chitosan is a natural polymer that has been used to prepare prolonged release nanoparticle formulations containing three antitubercular APIs [110]. Surface-modified PLGA nanoparticles with wheat germ agglutinin (WGG, a bioadhesive lectin) demonstrated sustained API release [111]. Also, PLGA nanoparticles containing insulin proved considerable sustained physiological efficiency [107].

Nanoparticle drug delivery systems are potential to target delivery of small molecules and macromolecules to specific cells and organs both *in vitro* and *in vivo* [96,106,112]. **Nanosized systems have been widely used to target specific tumor cells in cancer therapy.** Such targeted drug delivery is advantageous in terms of reducing the effective dose and side effects [111,112].

6. Techniques to prepare nanosized APIs

Methods for preparing nanocrystals can be classified into two main categories (Table 2): bottom-up techniques, where the molecules are built up, and top-down techniques, in which the crystals are commuted. A combination of top-down and bottom-up methods can also be used. Regardless of the preparation method, it is very important to understand the exposure/safety profile during development in order to administer the nanosized APIs safely in the clinic [36].

Table 2. A summary of some techniques (EPAS, evaporative precipitation into aqueous solution; HGCP, high gravity controlled precipitation; HPH, high-pressure homogenization; RESS, rapid expansion in supercritical fluid; SAS, supercritical anti-solvent; SFL, spray freezing into liquid) employed in the preparation of nanosized APIs.

Strategy	Technique	Methodology description	Examples
Bottom-up	Antisolvent precipitation (magnetic stirrer)	Drug is dissolved in an organic solvent and then it is mixed with an antisolvent (usually water).	[101,113]
	Sonoprecipitation	Crystallization by ultrasonic waves.	[100,113–119]
	HGCP	Precipitation under high gravity conditions usually obtained by using rotating packed bed.	[67,120–124]
	EPAS	Drug is dissolved in a low boiling point solvent. The solution is then heated above the boiling point and then sprayed in an aqueous heated solution containing a stabilizer.	[70]
	RESS	Drug is solubilized in a supercritical fluid and is expanded in a low-pressure area through a nozzle.	[125,126]
	SAS	Drug is dissolved in organic solvent, initiating the precipitation of solutes by antisolvent effect.	[65,127,128]
	SFL	Drug is solubilized in a mixture of aqueous/organic solvents with or without stabilizer then sprayed in liquid nitrogen, causing immediate precipitation.	[129]
Top-down	HPH	Drug particles suspended in a dispersion medium are passed several times through a high-pressure homogenizer.	[55,130–139]
	Wet milling	Drug particles are fed into a solution containing a stabilizer. The drug particles are then subjected to milling by glass beads.	[20,33,60,61,82,87,140–144]
	Salt-assisted milling	Drug particles are milled in the presence of a salt such as NaCl.	[145,146]
	Co-grinding	Drug particles are co-grinded with additives such as polymers.	[147–150]
Bottom-up followed by top-down	Precipitation–HPH	Drug particles are precipitated in the presence of an antisolvent and then processed by a high-speed homogenizer.	[151,152]
	Spray-drying–HPH	Drug particles are spray-dried and then processed by a high-speed homogenizer.	[153]
	Freeze-drying–HPH	Drug particles are freeze-dried then processed by a high-speed homogenizer.	[154]

6.1. Nanoprecipitation-dependant techniques

6.1.1. Principle

In nanoprecipitation, the lipophilic API is dissolved in an organic solvent, and then the resultant solution is added to an antisolvent (usually water or water-miscible antisolvent). Four steps are involved in this process: 1) chemical reaction (and the subsequent supersaturation), 2) nucleation, 3) solute diffusion and 4) particle growth [155]. This process is followed by phase separation to remove the organic solvent (e.g., by evaporation) and to isolate the API particles formed.

Supersaturation is obtained very rapidly due to the drowning-out effect of the antisolvent, which reduces solute solubility inducing its precipitation. The nucleation and particle growth are both dependent on the level of saturation [155]. Nanocrystal preparation methods using this technique can be classified according to the mixing type, solvent/antisolvent nature and the process used.

Micromixing is an important factor that may affect particle size of the product. Uniform micromixing may affect the concentration on the particle surface (*Ci*) as illustrated by Eq. 4.

$$\frac{dl}{dt} = Kg(Ci - C)^b \qquad \textbf{(Eq. 4)},$$

where *dl/dt* is the growth rate, *Kg* is the solute diffusion constant rate, *C* is the bulk concentration and *b* has the value between 1 and 3 (*b* value increases with temperature). Based on Eq. 4, an insufficient micromixing will lead to different nucleus growth rates and consequently a wide distribution of particle size [156]. The choice of solvent is critical because it may affect the physicochemical properties of the nanosized APIs produced [157].

6.1.2. Advantages

Nanoprecipitation is a relatively fast, simple and cost-effective technique [86] that is suitable for thermolabile compounds, and can produce a high yield of crystalline [79] and/or amorphous [158] nanosized APIs.

6.1.3. Disadvantages

Nanoprecipitation should be controlled precisely in order to control the size and the size distribution of the resultant nanoparticles.

Although some of the nanoprecipitation techniques have been successfully scaled up, the process of nanoprecipitation is not usually suitable for industrial scale-up [155]. Some of the nanoprecipitation equipment, such as those used in high gravity precipitation, are highly specialized and not widely available. Nanoprecipitation processes may require the control of potential residual solvents in the product. Nanoprecipitation suffers from the requirement of solvent recovery and the risk associated with the use of flammable solvents at high reaction temperatures. Some nanoprecipitation techniques, such as the hydrosol method, usually produce nanosized APIs with a wide distribution of particle size [159]. Additionally, nanoprecipitation suffers from batch-to-batch variability due to the rapid precipitation nature of this crystallization process.

6.1.4. Applications

Nanoprecipitation is involved in many pharmaceutical techniques such as pharmaceutical hydrosols [160], flash nanoprecipitation [121], sonoprecipitation [44,162] and high-gravity controlled precipitation [121,124,163].

6.1.4.1. The pharmaceutical hydrosol method

The pharmaceutical hydrosol method is a simple and a cost-effective method **that** has been used to produce **a wide range of** nanosized API particles with enhanced biological absorption, such as carotenoids (a mean size of 25 - 250 nm) [160], darodipine (a mean size of 116 nm) [164], progesterone (a mean size of 245 nm) [164], cyclosporine A (a mean size of 80 nm) [165], blue quinone (a mean size of 210 nm), red methine (a mean size of 310 nm) [166] and itraconazole (a mean size of 600 nm) [167]. **Hydrosols have also been successfully used to prepare nanosized carbamazepine and oxcarbazepine using static mixers [168,169].**

In brief, the lipophilic API is dissolved in an organic solvent, and subsequently a large amount of an antisolvent (usually water) is mixed with a macromolecule (such as gelatin and serum albumin [160]) and then added to the organic solvent with rapid mixing to guarantee fast nucleation of nanoparticles [170]. The mixing can be achieved by magnetic mixer yet there are more sophisticated equipment that could be used for industrial scale production [155]. Desolvating agents such as aqueous solutions containing multivalent ions (e.g., Ca^{2+} or SO_4) and hardening agents (e.g., aldehyde) may be added [171]. Pure insulin nanoparticles were also prepared using the pharmaceutical hydrosol method. Insulin was dissolved **in** a 0.01 N HCl

solution, and then it was titrated with a NaOH solution to the isoelectric point before it was diluted with deionized water. The subsequent nanoparticles were further agglomerated into microparticles by the addition of ethanol and stirring for 36 *h* at 300 rpm, making them suitable for pulmonary API delivery via dry powder inhalers (DPIs) [99].

Different stabilizers have been used to prevent the aggregation of the produced nanosized APIs, including polymers (e.g., polyvinyl alcohol (PVA), cellulose ethers, chitosan, agar, pectin, and gelatin), sugars (e.g., trehalose), and surfactants (e.g., poloxamers, partial fatty acid esters, polyoxyethylene fatty alcohol ethers and phospholipids) [167]. It is worth noting that polar stabilizers (such as dextra and hydroxyethyl starch) demonstrated a poor performance as compared with hydrophobic cellulose ethers. This may be explained as the cellulose ethers are more hydrophobic and, therefore, they interact with the surface of hydrophobic APIs better than the polar stabilizers, thus they provide a better protection for the APIs against aggregation [167].

6.1.4.2. Nanoprecipitation by acid-base reaction

Nanoprecipitation by acid-base reaction has been used to prepare nanocrystals of itraconazole, a poorly soluble compound in an aqueous solution with a pH-dependent solubility (solubility: 1 ng/mL at a **neutral** pH and 6 mcg/mL at a pH of 1). For example, Mou *et al*. [118] prepared itraconazole nanocrystals with a mean diameter of 248 nm. In brief, itraconazole was solubilized in an acidic aqueous solution containing ethanol. The precipitation process was induced by adding the latter solution to a solution of stabilizer in sodium hydroxide.

6.1.4.3. Sonoprecipitation

Sonoprecipitation technique has been used to prepare nanocrystals of several APIs such as simvastatin [114], fenofibrate [115], scutellarin [116], felodipine [117] and itraconazole [118] (Tables 3 and 4). By controlling the process variables, such as the sonication duration and intensity, sonoprecipitation can engineer nanosized APIs with controlled/improved physicochemical properties, such as particle size distribution (PSD), solid-state and dissolution rate [44,162]. For example, Chow *et al*. [119] reported that the dissolution rate of nanosized acetaminophen has decreased with increasing the concentration of an additive (p-acetoxyacetanilide) to a specific limit, after which the dissolution rate has increased. Budesonide nanoparticles suitable for inhalation were also produced using the sonoprecipitation method (Table 3). Budesonide was dissolved in acetone and the resultant solution was injected into water

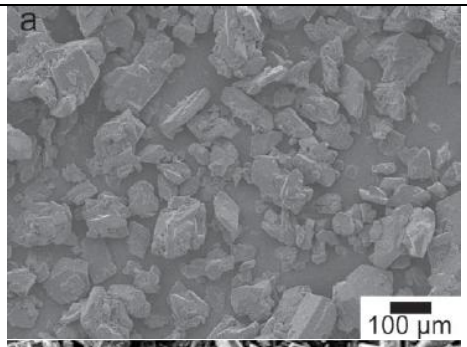
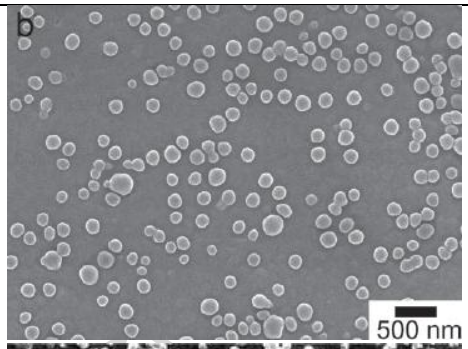
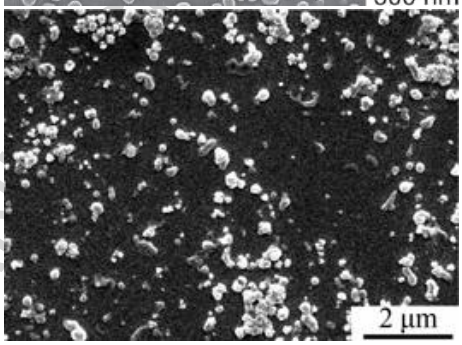
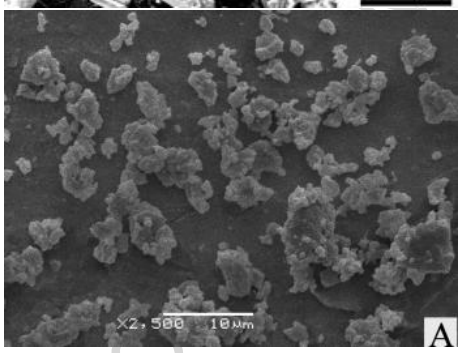
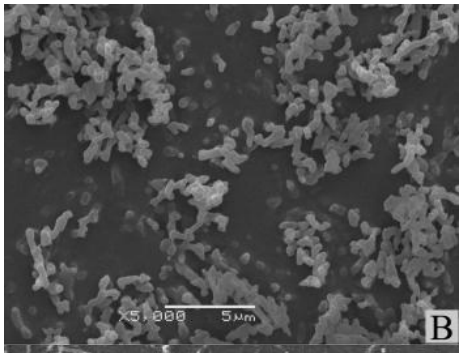
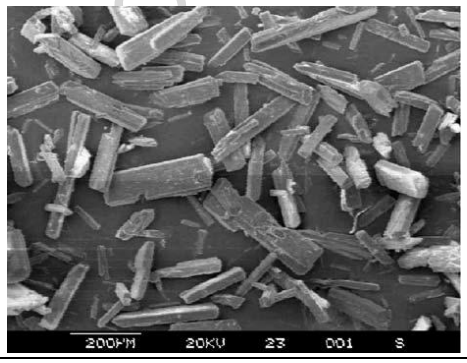
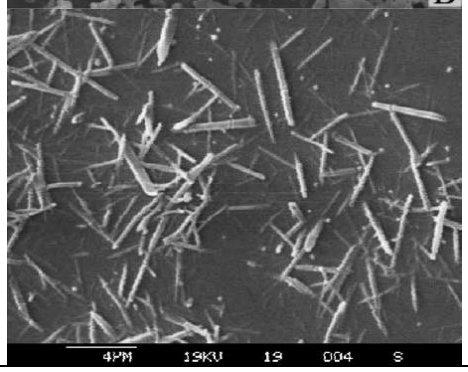
at a flow rate of 1 mL/min under sonication within an ice bath. A combination of hydrophobic (cetyl alcohol and span 85), hydrophilic (phospholipid (PL), PVA and polyvinylpyrrolidone (PVP)) and amphoteric (lecithin) surfactants were used to stabilize the formulations. Then, L-leucine was employed to prepare aggregations of the resultant budesonide nanoparticles suitable for pulmonary delivery, and with an improved dissolution rate in comparison to the commercial budesonide. Rod-shaped sonoprecipitated nanosized APIs showed a superior dissolution behaviour in comparison to milled nanocrystals [62,94]. Agglomerates of rod-shaped sonoprecipitated nanosized theophylline with a mean size suitable for inhalation (2.47 μm) were also prepared [94]. Sonoprecipitation has been used to prepare nanosized systems containing a combination of nanoprecipitated APIs. For example, El-Gendy and Berkland [100] prepared combinational chemotherapeutic dry powder aerosols via controlled nanoparticle aggregation. In the latter study, paclitaxel nanosuspensions were sonoprecipitated using various surfactants. The resultant nanosuspensions were then injected into a cisplatin solution to prepare a combination therapy of paclitaxel nanoparticles/cisplatin powders, which were agglomerated using L-leucine. The dissolution **of** the nanoparticles was significantly enhanced compared to the as received materials (Table 2). Sonoprecipitation usually gives variable yields depending on the operation conditions (e.g., ultrasound frequency/intensity, horn tip size, immersion depth, liquid volume, and time) [79,173].

Table 3. A summary of some nanosized APIs prepared by several techniques (sonoprecipitation, high gravity controlled precipitation (HGCP), wet-milling, high-pressure homogenization (HPH), spray-drying and supercritical fluid (SCF) technology) in the presence of several stabilizers (BSA, bovine serum albumin; HPC, Hydroxypropyl cellulose; HP–*β*–CD, 2-Hydroxypropyl-*β*-cyclodextrin; PVA, polyvinyl alcohol; PVP, polyvinylpyrrolidone; SDS, sodium dodecyl sulphate; TPGS, D–*α*–tocopherol polyethylene glycol succinate), and their main characteristics.

Technique	API	Category	Delivery system	Route	Mean size (SD) or size range (nm)	Solid-state	Stabilizer	Reference
Sonoprecipitation	Simvastatin	Lipid lowering agent	Nanosuspension	Oral	360 (9)	Partially crystalline	Poloxamer 188	[114]
	Fenofibrate	Lipid lowering agent	Nanosuspension	Oral	460 (20)	Crystalline	Poloxamer 188	[115]
	Scutellarin	Antioxidant	Nanosuspension	Oral	378 (28)	Crystalline	Polysorbate 80	[116]
	Felodipine	Antihypertensive agent	Nanosuspension	Oral	60-410	Partially crystalline	PVA or hypromellose	[117]
	Felodipine	Antihypertensive agent	Nanosuspension	Oral	140	Crystalline or amorphous	PVP and SDS	[113]
	Itraconazole	Antifungal	Nanosuspension	Oral	248 (15)	Crystalline before drying and amorphous after drying	Hypromellose	[118]
	Budesonide	Corticosteroid	Powder	Pulmonary	160-230	Partially crystalline	Lecithin, cetyl alcohol and pluronic F127	[119]
	Paclitaxel	Anti-tumor agent	Powder	Pulmonary	289-367	Amorphous	Cetyl alcohol, PVA, PVP, and lecithin.	[100]
HGCP	Azithromycine	Antibiotic	Nanosuspension	Oral	200 (20)	Amorphous	Soybean lecithin	[120]
	Salbutamol sulfate	β_2–adrenergic receptor agonist	Powder	Pulmonary	100-500	Crystalline	…	[67]
	Danazol	Corticosteroid	Nanosuspension	Oral	100-300	Crystalline	…	[121]
	Cefuroxime	Antibiotic	Nanosuspension	Oral	300	Amorphous	…	[122]
	Beclomethasone	Corticosteroid	Powder	Pulmonary	850	Crystalline	…	[123]
	Cephradine	Antibiotic	Powder	Pulmonary	200-400	Crystalline	…	[124]
Wet-milling	Danazol	Corticosteroid	Nanosuspension	Oral	169	Crystalline	PVP	[82]
	Naproxen	NSAID	Nanosuspension	Oral	270	Crystalline	SLS	[140]
	Naproxen	NSAID	Nanosuspension	Oral	328-536	Crystalline	1 % HPC and 1.2 % arginine	[60]
	Aprepitant	Anti-nausea	Nanosuspension	Oral	480	...	4 % HPC and 0.08 % SDS	[20]
	Ketoprofen	NSAID	Pellets	Oral	230-240	...	...	[87]
	Loviride	Anti-HIV	Powder	Oral	567 (25)	Partially crystalline	Tween 80 and poloxamer 188	[174]
	Cinnarizine	Anti-histamine	Nanosuspension	Oral	366 (12)	...	TPGS	[61]
	Phenylbutazone	NSAID	Nanosuspension	Oral	498 (10)	...	TPGS	[61]
	Griseofulvin	Antifungal	Nanosuspension	Oral	256 (1)	...	TPGS	[61]
	Indomethacin	NSAID	Nanosuspension	Oral	193 (2)	...	TPGS	[61]
	Mebendazole	Anthelmintic	Nanosuspension	Oral	190 (2)	...	TPGS	[61]
	Phenytoin	Anti-epileptic	Nanosuspension	Oral	406 (17)	...	TPGS	[61]

	Curcumin	Flavoring agent	Powder	…	250	Partially crystalline	…	[141]
	Cilostazol	Phosphodiesterase inhibitor	Nanosuspension	…	220	...	HPC and docusate sodium	[33]
	Iitraconazole	Antifungal	Nanosuspension	Oral	310 (130)	...	HPC and PVP	[144]
	Nifedipine	Antihypertensive	Nanosuspension	Oral	190 (70)	...	HPC and PVP	[144]
	Ibuprofen	NSAID	Nanosuspension	Oral	420 (80)	...	HPC and PVP	[144]
	Prednisolone acetate	Corticosteroid	Nanosuspension	Oral	70 (40)	...	HPC and PVP	[144]
	Itraconazole	Antifungal	Nanosuspension	Oral	549 (51)	Partially crystalline	Tween 80	[143].
	Zn-insulin	Antidiabetic	Nanosuspension	Parenteral	114	Amorphous	Pluronic F68 and sodium deoxycholate	[142]
HPH	Azithromycin	Antibiotic	Nanosuspension	Oral	400	Amorphous	Pluronic F68	[55]
	10-hydroxycamptothecin	Anti-cancer	Nanosuspension	Oral	131	Amorphous	Poloxamer 188	[130]
	Omeprazole	Proton pump inhibitor	Nanosuspension	Parenteral	<1000	…	Poloxamer 188	[132]
	Buparvaquone	Anti-parasite	Mucoadhesive hydrogel	Oral	600	Amorphous	Poloxamer 188 with or without lecithin or PVA	[131]
	Atovaquone	Anti-toxoplasmosis	Nanosuspension	Parenteral	279 (7)	…	Tween 80	[139]
	Amphotericin B	Anti-fungal	Nanosuspension	Oral	528	…	…	[138]
	Nimodipine	Antihypertensive	Nanosuspension	Oral	133-858	Mostly crystalline	Poloxamer 407	[137]
	Myricetin	Antioxidant	Nanosuspension	Oral	300-500	Amorphous	Soya lecithin, TPGS and/or HP–β–CD	[133]
	Revaprazan hydrochloride	Proton pump inhibitor	Nanosuspension	Oral	562 (16)	Partially crystalline	Poloxamer 188	[136]
	Itraconazole	Antifungal	Nanosuspension	IV	580 (18)	…	Poloxamer 188	[134]
	Curcumin	Anti-inflammatory	Nanosuspension	Oral	600	Amorphous	…	[135]
	Asulacrine	Topoisomerase II inhibitor	Nanosuspension	Parenteral	133 (20)	Crystalline	Poloxamer 188	[26]
Spray-drying	Iitraconazole	Anti-fugal	Powder	…	450	Crystalline	Poloxamer 188, deoxycholate and mannitol	[63].
	Fenofibrate	Antihyperlipidemic	Powder	Oral	553	Crystalline	SDS, hypromellose and mannitol	[64]
SCF technology	Phenytoin	Antiepileptic	Nanosuspensions	Oral	160	Crystalline	…	[175]
	Prednisolone	Corticosteroid	Nanosuspensions	Oral	230	Crystalline	SDS and PEG 4000	[176]
	Apigenin	Anti-cancer	Powder/capsules	Oral	400-800	Crystalline	…	[177]
	Tetracycline	Antibiotic	…	Oral	125-400	…	…	[178]
	Griseofulvin	Antifungal	…	Oral	130	Crystalline	…	[127]
	Ibuprofen	NSAID	Powder	Oral	25-276	Partially crystalline	PVP, PVA, SDS or BSA	[125]
	Cyclosporine	Immunosuppressant	Nanosuspensions	Oral/IV	400-700	…	Tween 80	[179]
	Paclitaxel	Anti-cancer	…	…	275	Crystalline	…	[180]
	Theophylline	Anti-asthmatic	…	Oral	85	Partially crystalline	…	[181]

Table 4. Scanning electron microscopy (SEM) photographs of some nanosized APIs prepared using high gravity controlled precipitation (HGCP) in comparison to their parent raw materials.

API	Raw material	Nanosized material	Reference
Azithromycine			[120]
Danazol			[121]
Beclomethasone			[123]
Cephradine			[124]

6.1.4.4. Nano-coprecipitation

It is also feasible to produce nanosized APIs by API-excipient nano-coprecipitation. For example, nifedipine nanoparticles were prepared by dissolving nifedipine and stearic acid in ethanol and then adding the subsequent solution to deionized water, allowing the precipitation of nanoparticle colloids exhibiting negative surface charge [101]. Sodium chloride (NaCl) was used to disrupt the electrostatic repulsion between the nanoparticles to achieve agglomerated nanoparticles of a controlled size and an enhanced dissolution performance. Nano-coprecipitation has been used to prepare nanosized APIs with different solid-states. For example, Lindfors *et al.* [113] prepared both amorphous and crystalline nanosuspensions of felodipine. Amorphous felodipine nanosuspensions were prepared by rapidly injecting felodipine dissolved in N, N-dimethylacetamide (DMA)) into an aqueous stabilizer solution (0.2% (w/w) PVP K30 and 0.25 mM sodium dodecyl sulphate (SDS)) in a vial placed in an ultrasonic bath. Miglitol was added to the felodipine API solution at a felodipine:miglitol ratio of 4:1 (w/w) to inhibit Ostwald ripening. Crystalline felodipine nanosuspensions were prepared using a same procedure but with 30 min sonication time and without adding miglitol. The amorphous nanosized felodipine nanoparticles demonstrated much higher solubility in comparison to the crystalline nanosized felodipine. The stability of the amorphous nanosuspensions was very sensitive to the presence of tiny amounts of the crystalline form.

6.1.4.5. High gravity controlled precipitation

High gravity controlled precipitation (HGCP) has also been used in nanoprecipitation (Table 2). In this method, the solution going through the rotating packed bed (RPB) packing is atomized into very fine droplets, threads, and thin films under the high shear field where micromixing take place [129]. The HGCP method can be run in two modes: high gravity reactive precipitation (HGRP) (where two reactants form nanocrystals under high gravity) and high gravity antisolvent precipitation (HGAP) (where a solvent-antisolvent reaction takes place under high gravity). The HGRP method, invented by Chen *et al*., [183], was first used to produce nanocrystals of an inorganic compound, i.e., $CaCO_3$. Chen *et al*. [163] demonstrated the capability of the HGRP method to produce nanosized APIs using benzoic acid as a model API. The main factors that affect the size of the HGRP engineered nanosized APIs were shown. Particle size decreased with increasing bed speed, concentration and volume flow rate of the reactants. Particle size was decreased from 600 nm to ~ 50 nm when increasing the bed speed from 15 Hz to 20 Hz.

However, no significant decrease in particle size was observed when a bed speed above 20 Hz was used. A similar trend was observed regarding the influence of flow rate of the reactants on particle size. Finally, increasing the concentration of HCl from 0.1 to 0.5 mol/L has decreased the particle size of benzoic acid from 70 nm to 10 nm.

The HGRP method has been applied to prepare nanosized APIs such as azithromycin [120] and salbutamol sulphate [67] (Table 4). The HGRP engineered azithromycin nanocrystals showed a mean particle size of 300-500 nm and ~ 90% dissolution rate after 15 min in comparison to a 50 % dissolution rate obtained from for the raw material [120]. The HGRP engineered salbutamol sulphate nanocrystals, prepared by vigorous mixing of an isopropanol solution of salbutamol sulphate with sulfuric acid in RPB, demonstrated a mean size between 100 and 500 nm. These nanocrystals were further spray-dried to form agglomerates of a mean diameter of 2 µm suitable for inhalation via DPIs [67]. The HGRP method is convenient, cost-effective and suitable for the industrial production of nanosized APIs. However, a by-product might be produced restraining the overall process [129].

In contrast to the HGRP method, the HGAP method does not often produce by-products. However, the HGAP progress may require a large amount of organic solvents [129]. The HGAP method was used to prepared nanosized danazol that demonstrated a mean size of 100-300 nm and a dissolution rate of 80 % after 5 min in comparison to 30 % dissolution rate obtained from the raw danazol [121]. In brief, danazol was dissolved in ethanol and then mixed with an antisolvent (water) by RPB. The HGAP method was also utilized to produce nanosized cefuroxime with an enhanced dissolution rate, making it suitable for oral administration [122]. Inhalable beclomethasone with a mean size of 850 nm and an enhanced DPI aerosolization performance was engineered using HGAP [123].

Many scientists added further adaptations to the HGCP method. For example, Baxter Inc. patented the Nanoedge® that involved precipitation coupled with a high energy process [184]. In this method, the API was dissolved in a water-miscible solvent, to which an antisolvent was added and then energy (heat and/or mechanical stress) was introduced to the resultant mixture to form particles with a mean size between 400 nm and ~ 2 µm. High energy was also used to convert the unstable/metastable API forms (e.g., amorphous, semicrystalline or supercooled liquid form) to stable crystalline API forms [134]. A combination of HGRP and HGAP methods

was used to engineer nanosized cephradine particles with a mean size of 200-400 nm and a fast dissolution rate [124].

6.2. Milling-dependent techniques

6.2.1. Wet milling technique: The NanoCrystal® technology

6.2.1.1. Principle

Wet milling, or commercially known as the nanocrystal technology, is an aqueous based top-down milling process in which nanosized APIs (usually smaller than 400 nm) can be obtained by demoting microsized APIs into the nanodimensions [185,186]. This attrition process is achieved in the presence of surface modifiers or grinding media [140]. Grinding media with a size of ≤ 1 mm are usually preferred in order to impart less wear to the mill [140]. The process could be achieved either with [14] or without [187] high energy input. The high-energy milling is regarded as a universal procedure to produce nanocrystals. The API powders, usually in micro-size, are charged to a milling chamber, which contains milling beads that are moved by either electric or magnetic stirrer (Figure 1).

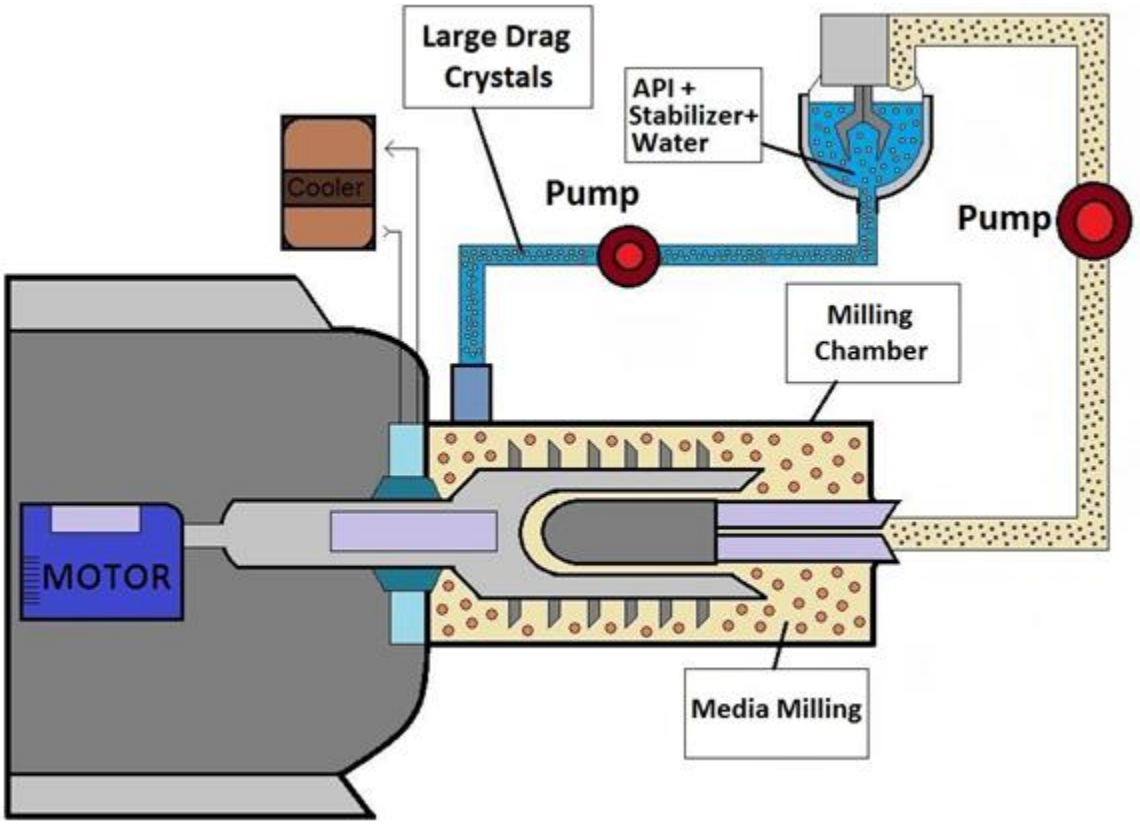


Figure 1. A schematic representation of the Media Milling Process, modified from Merisko-Liversidge et al. [27].

Nanosized APIs may be achieved following ~ 30–120 min milling [188]. The API:stabilizer ratio usually ranges between 2:1 and 20:1. A suitable amount of a stabilizer has to be used in each formulation, i.e., the use of a high amount of a stabilizer may promote Ostwald ripening, whereas the use of a too little amount of a stabilizer may lead to aggregation [27]. Common stabilizers used include cellulosic, pluronics, polysorbates and povidones. It is also common to use a combination of ionic and non-ionic stabilizers [27].

Ghosh *et al*. [189] studied the process factors that may affect the success of the ball milling in the term of particle size-reduction. The rotation speed of the planetary ball mill was shown to be the most important factor that affects the particle size of the milled products. For example, the mean particle size of a nanosuspension was reduced from 1400 nm to 400 nm when the rotation speed of the planetary ball mill was increased from 150 rpm to 400 rpm. George and Ghosh [190] studied the effect of material property variables that affect the critical quality attributes (CQAs) of the nanosuspensions produced. In order to determine the most suitable candidate API for media milling, a correlation between the mechanism of stabilization and API properties was established. It was concluded that APIs with high enthalpies and high hydrophobicities, that can be stabilized either electrostatically or sterically, would be good candidates for media milling, and the choice of a stabilizer is influenced by the hydrophobicity of the API (Figure 2).

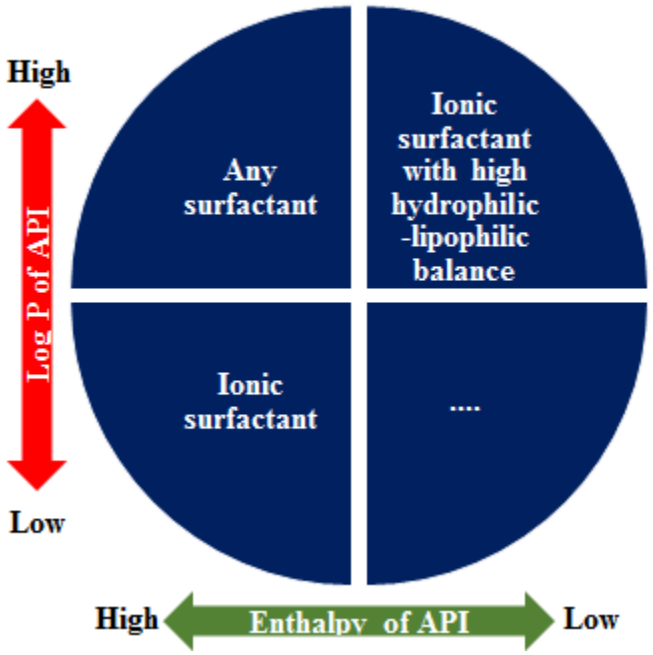


Figure 2. The strategy of choosing a suitable stabilizer based on API properties [190].

Nakach *et al*. [191] performed a systematic approach to select the best type/concentration of stabilizer during nanoparticle engineering. It was found that SDS and PVP at a ratio of 40:60 (w:w) and a total concentration of 1.2% w/w lead to nanosuspensions with the best stability profiles.

6.2.1.2. Advantages

Wet milling technique is a leading method to preparing poorly soluble nanosized APIs with narrow PSDs [188]. The process is simple and requires few components, i.e., micronized API particles, water, and a stabilizer. The method is versatile and suitable especially for APIs with a solubility of less than 200 µg/mL [192].

High API loads could be achieved, thus this technology has been successfully used in the commercial context [193]. The safety of the nanosized APIs produced by wet milling has been established, as reviewed elsewhere [194]. For example, wet-milled nanosized UG558 (a poorly soluble API) [195], AZ68 (a neurokinin NK receptor antagonist) [196] and paclitaxel [52] have all been successfully formulated into injectable dosage form and none of these APIs showed an adverse effect during animal studies. Nanosized naproxen produced by wet-milling showed less gastric irritation in comparison to conventional oral dosage forms [140].

Wet-milled nanosized APIs demonstrated an increased bioavailability (as indicated by an increased C_{max}, a reduced time to maximum plasma concentration (T_{max}) and an increased AUC) and a reduced fasted/fed variability [51,82,87,140,195,196]. Some wet-milled nanosized APIs, such as 1, 3-dicyclohexylurea, showed similar pharmacokinetics to those observed for a solution when studied in rats [197].

Nanosized APIs processed by wet milling demonstrated a higher physical stability and a reduced batch-to-batch variability in comparison to APIs processed by other methods such as microfluidic precipitation [198]. Wet milling may provide a suitable platform for targeted delivery of insoluble APIs or diagnostic agents [192].

6.2.1.3. Disadvantages

Wet milling is a time-consuming process that may require hours to days to reach the required nanosize range depending on the API and the mill type [187]. Additionally, solid-state alteration (e.g., polymorphic transition or chemical degradation) of the APIs may occur during milling [199]. For example, long milling times may induce the formation of amorphous content that

raises stability concerns [200–202]. Therefore, nanomilling should be performed under controlled temperature conditions, and solid-state and chemical stability analyses should be conducted before and after wet milling. The use of milling media containing glass or zirconium oxide could cause a trace of contaminants to the milling chamber [203,204], thus cross-linked polystyrene beads were suggested as an alternative milling medium [27,41].

Based on the DLVO theory, nanosized API particles have exceedingly high free energy, attributable to their high surface area, and consequently they have a high tendency to agglomerate [84]. Ostwald ripening observed in wet-milled nanosized APIs is another potential drawback [24], in which an API tends to solubilise in water, and then it is crystallized to large particles present in nanosuspension. The latter limitations could be avoided by using a carefully selected stabilizer [39]. An ideal stabilizer should prevent the aggregation of the nanosized API without negatively affecting its solubility.

6.2.1.4. Applications

Wet milling has been extensively used to prepare many nanosized APIs, as summarized in Table 3. For example, in one study, a fast production of sub-100 nm particles of griseofulvin and indomethacin was achieved by an intensified wet stirring media milling using small beads [205].

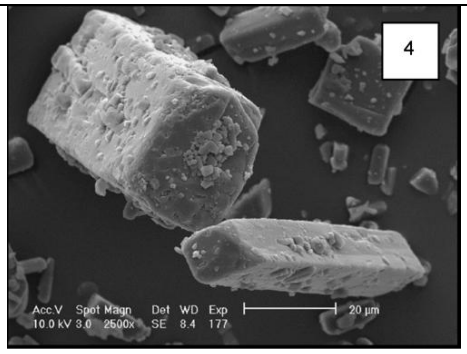
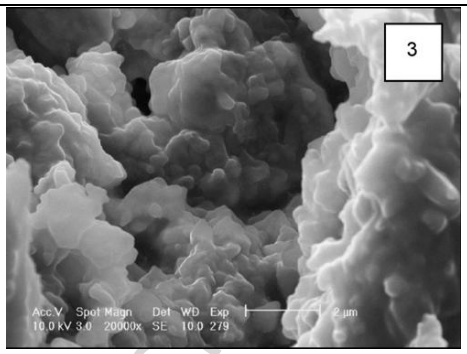
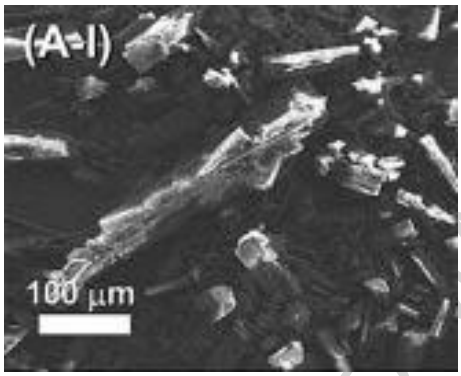
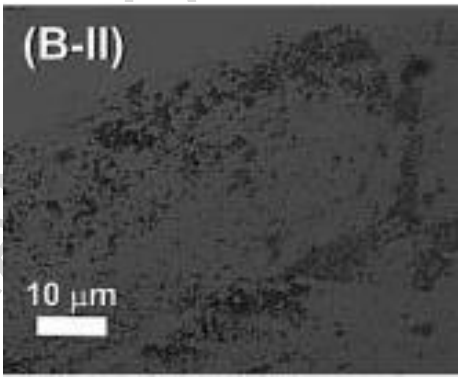
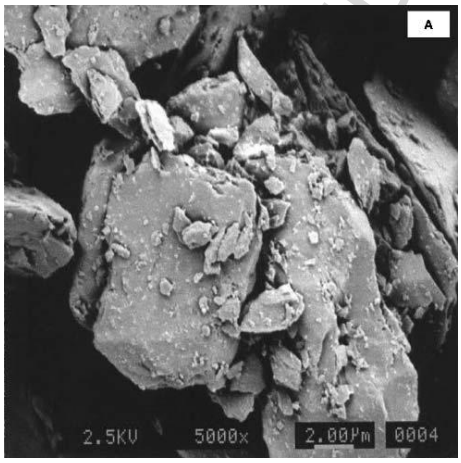
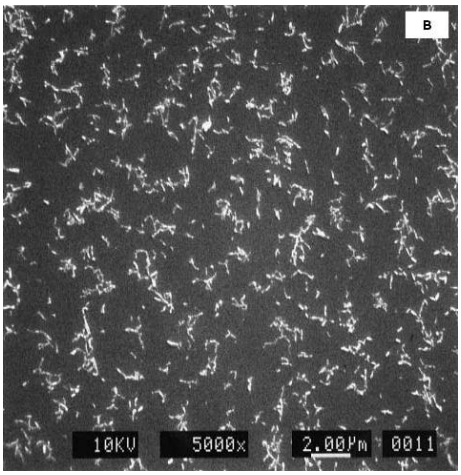
Different stabilizers were used during the preparation of wet-milled nanosized APIs, including PVP [82], pluronic derivatives [140,192], PVA [60], vitamin E, polyethylene glycol, *d–α–* tocopherol polyethylene glycol succinate (TPGS) [61,206] and sodium lauryl sulphate (SLS) [87].

Six products employing the nanocrystal technology are currently available on the market, i.e., Rapamune®, Emend®, Megace® ES, TriCor® 145/48, Invega® and Sustenna® [154].

In general wet milling is used to produce nanosized APIs with enhanced pharmaceutical performance, improved safety profile and improved patient compliance [188] (Table 5). Indeed, the dissolution enhancement was the main outcome of several studies [33,87,174,207,208]. Wet milling has been used to resolve some safety-related issues of some antitumour APIs, such as etoposide and paclitaxel. Additionally, wet milling has enabled formulation scientists to produce several injectable products for the first time of some poorly soluble APIs such as piposulfan and camptothecin [192]. Wet-milling was successfully employed in the preparation of itraconazole-adipic acid nanococrystals (in the presence of Tween 80® as a surfactant) with an enhanced dissolution rate in comparison to amorphous API delivery systems [143]. The preparation of

biologically active nanosized peptide particles has also been feasible using the wet milling technology. For example, Zn-insulin nanoparticles with a mean diameter of 150 nm and a narrow size distribution were produced in the presence of pluronic F68, SDC and water at a neutral pH [142] (Table 5).

Table 5. Scanning electron microscopy (SEM) or polarized light microscope (PLM) photographs of some nanosized APIs prepared using wet-milling in comparison to their parent raw materials.

API	Raw material	Nanosized material	Reference
Loviride			[174]
Curcumin			[141]
Zn-insulin			[142]

6.2.2. Salt-assisted milling

Salt-assisted milling with steel balls has been shown as a promising approach to producing nanosized APIs [145,146]. The process is similar to that used in wet ball milling except that additional excipients such as NaCl are employed in the milling medium to prevent nanoparticles from degradation [146]. NaCl has been used because it is hard enough to crush soft organic API materials, helps to prevent the API particles from aggregation, a water washable material, inexpensive and a 'generally recognized as safe' excipient. For example, NaCl has been used as a milling assistant to produce stable nanocrystals of fenofibrate, a model lipophilic API (log *P* = 5.24) [209] that is virtually insoluble in water (solubility ~ 0.42 mg/L at 25 ºC) [210]. Milling efficiency has been shown to be dependent on the rotation speed, fenofibrate:salt ratio and milling time. In another research, sugar has been employed to stabilize a nanodiamond powder [145].

6.2.3. Co-grinding

Cogrinding is a simple technique that involves grinding APIs with specific additives [147]. Cogrinding with different additives has been extensively used to prepare nanosized APIs with enhanced dissolution rates [82,149,211,212]. For example, pranlukast [147], ONO-8713 (a specific EP_1 antagonist) [148], indomethacin, furosemide and naproxen [147] were cogrinded with cyclodextrins as grinding additives to produce nanosized APIs with enhanced stability profiles.

Hydroxypropyl cellulose (HPC) [149] and dextrin [150] were used as cogrinding additives to produce nanoparticles under suitable water content conditions. The amount of added water has been shown as an important factor that has a considerable influence not only on the size but also on the stability of the nanosized API preparation. The absence of water could lead to a lack of interaction between indomethacin (as an API) and dextrin (as an additive) leading to nanoparticle aggregation [150].

6.3. High-pressure homogenization

6.3.1. Principle

High-pressure homogenization (HPH) is a milling technique that employs a high pressure as the main force to produce nanosized APIs. The API particles are usually suspended in a dispersion medium and then passed several times through a high-pressure homogenizer (Table 1).

Typically, the applied pressure is increased step-wise from 10% to 100% in order to avoid clogging of the narrow homogenization gap. The factors that may affect the nanosuspensions when being homogenized include fluid shear, particle collision and cavitation [213]. Two equipment have been principally employed to produce nanocrystals using high pressure, the Microfluidizer [214] and the piston-gap homogenizer [215].

The Microfluidizer is a jet stream technique, in which an API is suspended in a dispersion phase (usually water) and then pumped into either Z or Y chamber where collision forces are the main attributes by which the size of the API particles is reduced [216,217] (Figure 3).

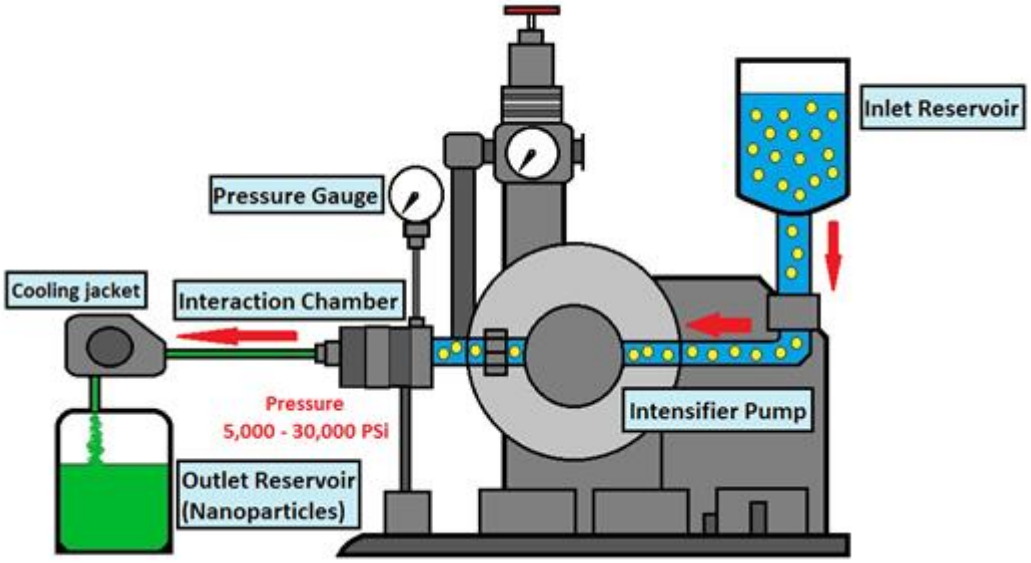


Figure 3. A schematic diagram of the Microfluidizer setup, modified from Jafari et al. [217].

In the piston-gap homogenizer, either aqueous or non-aqueous media could also be used as the main dispersion phase [218]. In both cases, API particles are charged into a cylinder and then passed through a gap of 25 µm. Although cavitation is considered the main important factor of nanocrystal production, the PSD of the resultant nanosized API is dependent on many factors, including the pressure applied, the number of homogenization cycles and the toughness of the API particle [132]. **For example, increasing the homogenization pressure from 500 bar to 1500 bar has been shown to lead to a decrease of the d_{90}% (particle size at 90% volume distribution) of a model drug (RMKP 22) from 7.2 µm to 5.6 µm after five cycles** [25]**.**

The polydispersity index of the prepared particles decreased with increasing the number of cycles applied. The number of particles with a mean diameter higher than 5 µm has been shown to decrease with increasing the processing time. Furthermore, the properties of the nanoparticles prepared are dependent on the API processed. For example, cube-shaped, rod-shaped and needle-shaped nanosized particles were prepared for RMKP 22, prednisolone and RMKP 23 respectively, although an identical protocol was applied [25].

6.3.2. Advantages

The HPH method has been broadly used to produce functionalized nanosized particles for versatile applications in food [219], cosmetics [220] and pharmaceutical [221] industries. The HPH has been used to engineer poorly soluble nanosized APIs with enhanced dissolution rates [222], excellent uniformities and improved dispersibilities [223]. **High API loading SLNs with rapid dissolution rates of class II API substances** [224] **were prepared using the HPH method. There are also reports where the amorphous and crystalline forms coexist in SLNs made by HPH** [225]**.**

The HPH method is suitable for the continuous production of nanoparticles on both laboratory and industrial scale [226]. It can be also used for the production of both immediate and controlled release nanosized pharmaceuticals [227–231]. For example, spherical poly(d,l-lactide-co-glycolide) (PLGA) nanoparticles (200 – 300 nm) for controlling the release of paclitaxel were prepared using the HPH method [223]. Long-term stable budesonide nanoparticles suitable for nebulization were also successfully produced [232].

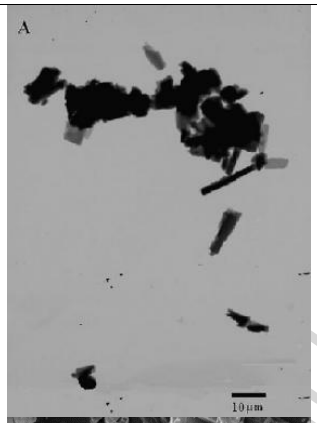
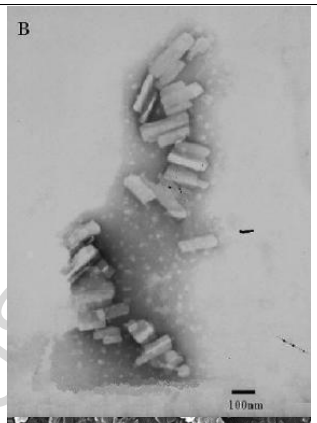
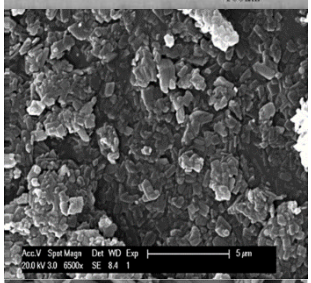
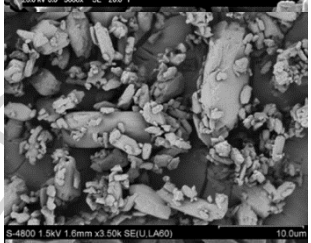
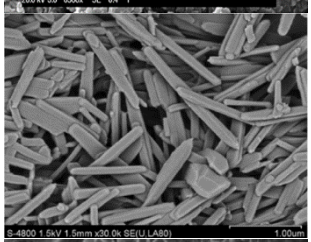
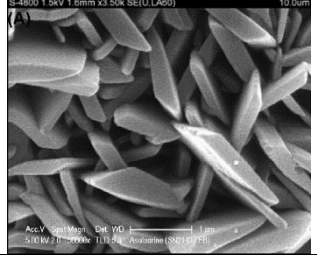
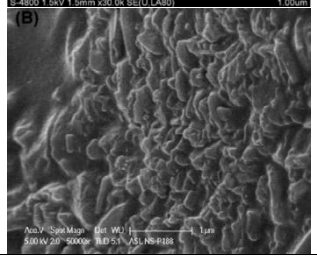
6.3.3. Disadvantages

Many process cycles may be needed to produce nanosized APIs in the desired particle size [25]. Additionally, polymorphic form transformation associated with the preparation of nanosized APIs using HPH technique could be a challenge. For example, some HPH-processed nanosized APIs were shown to be amorphous [55,130] and, therefore, sever concern about their stability is justified [29]. In such case, alternative methods may be considered. For example, in one study, the ultrasound homogenization method was as appropriate as the HPH method for the preparation of SLNs [233].

6.3.4. Applications

The HPH method has been extensively used to enhance the dissolution rate of several poorly soluble APIs such as azithromycin [55], 10-hydroxycamptothecin [130], omeprazole [132], buparvaquone [131], atovaquone [139], myricetin [133], revaprazan hydrochloride [136] and asulacrine [26] (Table 3). The HPH method has been used to prepare nanosized APIs with different morphologies. For example, rod-shaped (e.g., nimodipine [137], myricetin [133], revaprazan hydrochloride [136] and itraconazole [134]), spherical (e.g., curcumin [135]), and irregular-shaped (e.g., asulacrine [26]) nanosized API particles were prepared using the HPH method (Table 6). Regardless of particle shape, the decrease in particle size of the nanosized APIs has been consistently associated with an enhancement of the dissolution rate of the resultant nanosized APIs [226,234]. A combination of high speed homogenization and HPH was also used to prepare nanosized tobramycin nanoparticles suitable for DPIs. The high-speed homogenization was used as a pre-treatment step for the reduction of particle size [235].

Table 6. Scanning electron microscopy (SEM) or transmission electron microscopy (TEM) photographs of some nanosized APIs prepared using high-pressure homogenization (HPH).

API	Raw material	Nanosized material	Reference
10-hydroxycamptothecin			[130]
Myricetin			[133]
Revaprazan HCl			[136]
Asulacrine			[26]

6.4. Spraying-dependent techniques

6.4.1. Spray-drying

6.4.1.1. Principle

Spray-drying is the transformation of a liquid or a dispersion feed from the liquid state to a powdered solid phase by spraying the feed into a hot drying medium [236]. The technique involves two main steps: atomization followed by drying [237].

The Büchi Nano Spray Dryer B-90, innovated by Li *et al* (2010), has been used to produce a high yield (~ 70% to 90%, w/w) of nanosized APIs. The new modified technology uses a vibrating mesh to create droplets in a size range smaller than the traditional spray dryer [238,239] (Figure 4). The average size of the nanosized particles produced using this technology usually ranges from 500 to 2500 nm. The diameter (*d*) of a spray-dried nanoparticle can be predicted using Eq. 5 [155].

$$\boldsymbol{d = D\sqrt[3]{\frac{C}{\rho}}} \qquad \textbf{(Eq. 5)},$$

where *D* is the drop diameter, *C* is the solution concentration and ρ is particle density.

The physicochemical properties of the spray-dried APIs are dependent on several process parameters such as the inlet temperature, the chamber's internal moisture content and the liquid feed rate [240]. The spray-dried pharmaceutical material suffers from thermal stress, which could significantly affect the material's critical quality attributes (CQAs) [241].

Usually, spray-drying produce amorphous dispersion systems of poorly soluble APIs [242]. Such systems have the drawback of insufficient stability. Nevertheless, the solid-state of the spray-dried particles depends on formulation factors (e.g., feed concentration or solvent type) and process factors (e.g., drying gas flow rate or solution spray rate) [242], and it ranges from completely amorphous, semi-crystalline to crystalline forms [243]. For example, spray-dried naproxen showed no amorphous form, whereas spray-dried indomethacin showed different forms of different stabilities [241].

6.4.1.2. Advantages

Spray-drying can successfully replace freeze-drying in the manufacturing of nanosized parenteral APIs. Spray-drying allows good control of particle's physicochemical properties due to the

ability to change several parameters during the spray-drying process such as temperature, nozzle design, etc. Additionally, spray-dried products require shorter processing times in comparison to freeze-dried products [244,245]. In contrast to freeze-dried products, spray-dried products are typically fine and free-flowing powders [245].

6.4.1.3. Disadvantages

One main disadvantage of spray-drying is the cost of settings and maintenance [246]. Complex biological molecules, such as proteins, are difficult to spray dry because of their sensitivity to the high shear stress during the atomization step, which could destabilize labile materials. The amount of shear stress encountered depends on the type of atomizing and the atomizing pressure used. In general, spray-drying of proteins has been a challenge because of the absence of specific process guidelines, thus often a trial-and-error process is used rather than rational Quality by Design principles [247]. Spray-drying mostly generates amorphous products, thus the production of stable APIs by spray-drying may be a challenge [248]. The spray-drying method can give different yields depending on the conditions applied [241]; nevertheless, a low yield is usually associated with the spray-drying process due to the loss of the product on the walls. The production of nanoparticles by spray-drying is limited not only by the low separation capacity of the cyclone but also by the inadequate forces of liquid atomization [249].

6.4.1.4. Applications

Spray-drying is a well-established technique that has been used for a century in different areas including food manufacturing, fertilizers, oxide ceramic and pharmaceutical processing [250]. In the pharmaceutical industry, spray-drying has been used for the preparation of oral and inhaled products, pulmonary delivery of proteins and vaccines, and for the processing of viable organisms [251]. Recently, there has been increased attention to the use of spray-drying as a particle engineering technique for the size-reduction of APIs [252] (Table 3). The production of spray-dried nanosized APIs is one approach to overcome the stability and dissolution rate issues associated with spray-dried microsized APIs. For example, Yin *et al*. [253] used the spray-drying method to prepare nanosized crystalline BMS-347070 (a COX-2 inhibitor API) (in the presence of pluronic F127) with increased dissolution rate and bioavailability in comparison to the micronized BMS-347070. Mizoe *et al*. [254] utilized 4-fluid nozzle spray drier to produce

microparticles containing nanosized pranlukast that showed promising properties for pulmonary, oral and parenteral delivery.

6.4.2. Nanoprecipitation–spray drying

The continuity and scalability of the spray-drying method to produce nanosized formulations were investigated by coupling solvent-antisolvent precipitation with immediate spray-drying [64]. For example, Hu *et al.* [64] coupled nanoprecipitation and spray-drying to prepare crystalline nanosized fenofibrate particles with enhanced stability and dissolution rate behaviours in comparison to physical mixtures. SDS and hypromellose were used as stabilizers, whereas lactose or mannitol was used as resdispersants.

Nanospray-drying is a convenient method to prepare controlled submicron API delivery vehicles useful for pulmonary application, potentially allowing access to the alveolar tissue [105]. A combination of nanoprecipitation and spray-drying methods has enabled scientists to develop large porous nanoparticles for the delivery of hydrophobic APIs. The so-called 'Trojan particles', developed by Tsapis *et al*. [95], could offer the advantages of both nanoparticle systems and large porous particle systems in terms of better flow and dissolution rate properties.

6.4.3. Ionotropic gelation–spray drying

Chitosan undergoes a gelation reaction when it interacts with a polyions such as sodium tripolyphosphate (TPP) [255]. For example, chitosan/TPP nanoparticles were prepared based on the ionotropic gelation of chitosan with TPP. In brief, both chitosan and TPP were dissolved in water. The nanoparticles were immediately formed upon mixing the TPP solution with chitosan solution. Then, an alkaline solution of insulin was mixed with the TPP solution to form insulin-loaded chitosan/TPP nanoparticles, which were then mixed with mannitol and subsequently spray-dried [97]. This method produced biocompatible nanoparticles suitable for pulmonary delivery of APIs. For example, this method was used to prepare chitosan nanoparticles that showed a compatibility with respiratory epithelial cells [256].

6.4.4. Aerosol flow reactor

The aerosol flow reactor (AFR) is a single step process that can produce nanosized APIs **with** narrow size distributions. The API is dissolved in a volatile biocompatible solvent and then atomized into a gas carrier. Nanoparticles are formed while the solvent is evaporated using a heated laminar flow tube [257–259]. The size of the resultant nanoparticles is dependent on

several process factors, such as the temperature, solution concentration, atomizer design, API solubility and API-solvent interaction [260]. For example, Eerikäinen *et al* [257] studied the effect of temperature on the size of the AFR engineered nanosized beclomethasone. No significant difference in particle size was observed when the temperature was between 40 and 120 ºC. However, a significant increase of particle size was observed at temperatures above 120 ºC, whereas a reduced particle size was obtained at temperatures above 160 ºC. The AFR method allows the direct preparation of nanosized APIs in the powder state. For example, nanosized powders (mean size of ~ 90 nm) consisting of a poorly soluble corticosteroid (beclomethasone dipropionate) and polymeric materials (e.g., Eudragit E 100 or Eudragit L 100) were successfully prepared [257]. However, the AFR method may not be suitable for heat labile APIs and the yields obtained depend mainly on nozzle design [258].

6.4.5. Emulsification–spray drying

Nanosized API spheres can be produced by simple emulsification, which enhances the encapsulation of highly soluble APIs such as proteins, followed by spray-drying. For example, Kawashima *et al*. formulated peptide nanospheres by diffusion of acetone from an organic phase containing chlorinated hydrocarbons to an aqueous phase containing nafarelin acetate (API) and PLGA. The same research group applied a modified method, in which methanol was replaced by chlorinated hydrocarbons in order to improve the encapsulation efficacy of peptide APIs and minimize the preparation time of less than 3 *h*. Nanosphere suspensions, consisting of PLGA, acetone, methanol and the API with PVA solution, have been prepared by mixing under agitation [107,261].

6.4.6. Electrospraying

Nanosized API formulations can be prepared by spray-drying utilizing an electrohydrodynamic force instead of pressurized air stream for atomization [262] (Figure 4). Applying a high electric field will lead to an accumulation of electrical charge in the nozzle and eventually a cone-shape (‘Tylor cone’) is formed [263,264]. For example, electrospraying has been used to prepare nanosized naproxen with a mean diameter of 100 nm using an applied voltage of 2.7 kV [265]. It was shown that the redispersability of the nanoformulations is influenced by the voltage applied, whereas the particle shape and degree of crystallinity were independent of the electrical field applied.

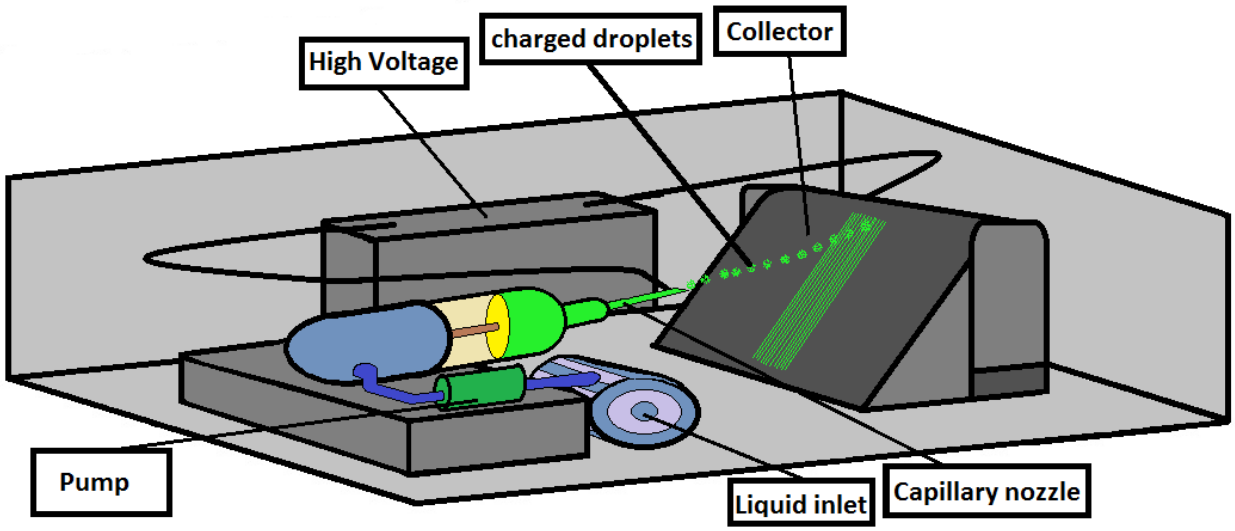


Figure 4. A schematic diagram of the preparation of the electrospray setup, modified from [252] (diagram not down to scale).

6.5. Supercritical fluid technology

6.5.1. Principle

A supercritical fluid (SCF) is any material at a temperature and pressure above its critical point. A SCF has both the solvation ability like liquids and the effusion ability like gasses. SCFs are highly compressible and their solvation ability can be controlled by manipulating the temperature and/or pressure applied during processing [266]. SCFs are increasingly used to prepare nanosized poorly soluble APIs (typically smaller than 300 nm) **by** controlling the pre-expansion temperature and pressure [267,268]. A common method includes the rapid expansions of supercritical solutions (RESS) [269], in which the API is dissolved in a SCF that is then expanded into a low-pressure chamber through a nozzle. The differences in the pressure between the two chambers allow the API to precipitate [269]. This method has been modified by dissolving the API in a liquid to which a SCF is added as an antisolvent that causes API precipitation of the API [270,271]. Depending on the method of crystallization, SCF technology can be classified into three main processes: gas anti-solvent (GAS) [272], aerosol solvent extraction system (ASES) process and solution-enhanced dispersion by SCFs (SEDS) [270].

6.5.2. Advantages

SCF technology could offer several distinct characteristics in their application within the pharmaceutical area, including micronization and modification of particle physical properties. By manipulating the conditions of the process either micro- or nano-particles could be obtained [126]. SCF technology is organic solvent free, easy to scale-up, flexible, and offer the opportunity to control the size and morphology of the nanosized APIs produced [260,273]. Supercritical CO_2 offers many advantages over other SCFs, because it is nontoxic, inexpensive, innocuous, nonreactive, noninflammable, environmentally friendly, and has a relatively low critical point and a moderate critical pressure [270].

6.5.3. Disadvantages

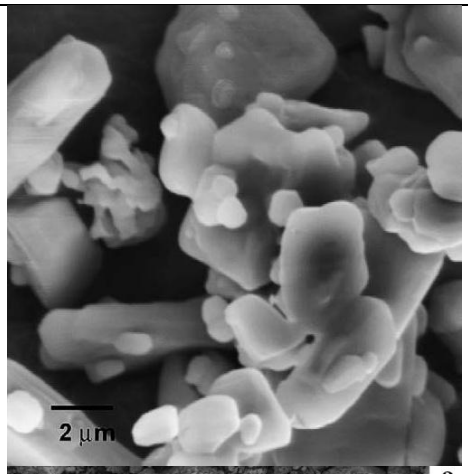
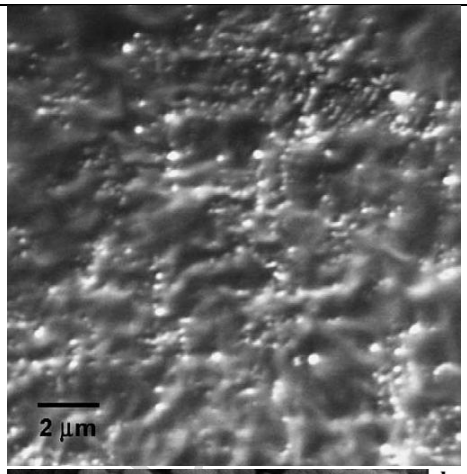
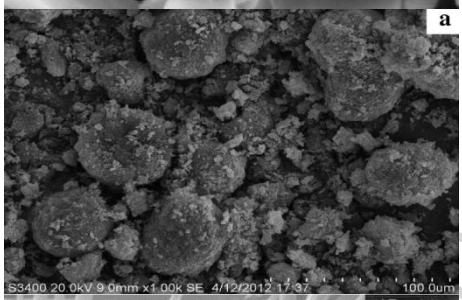
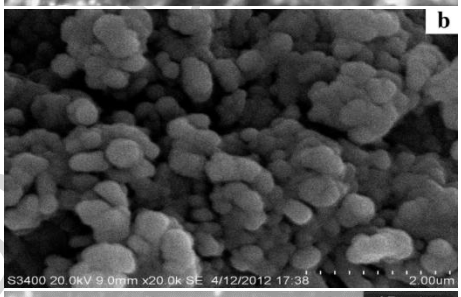
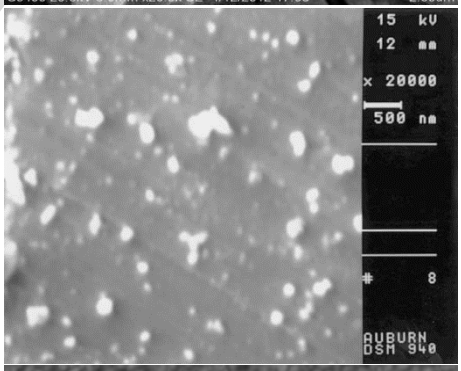
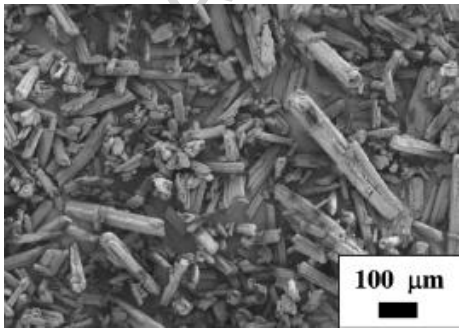
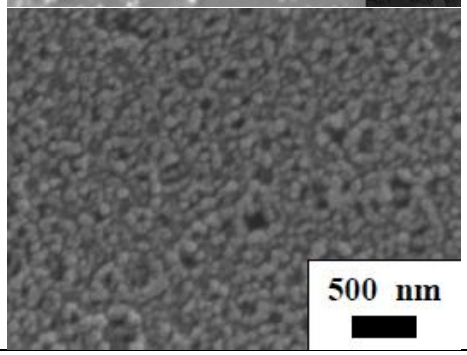
Possible denaturing effects of the solvents or the antisolvents used in SCF technology may cause some concerns. The SCF processes usually require long production times [155], although some recent methods utilize cosolvents to overcome this limitation [175]. The low solubility of most polar APIs in CO_2 is one main drawback to SCF technology, making it unsuitable for APIs showing poor stability in the aqueous phase. To this end, methanol was used as an alternative

SCF, in which the solubility of a polar API could be increased [175]. Moreover, concerns about the presence of residual co-solvents should be investigated [274]. Furthermore, SCF technologies usually produce nanosized API particles with broad size distributions, and contamination with microparticles is usually encountered [270]. Finally, nanosuspensions prepared by SCF technology may demonstrate short-term stability [260].

6.5.4. Applications

The dissolution rate enhancement of poorly soluble APIs is one of the most important applications of SCF [275]. For example, a threefold enhancement of the dissolution rate of phenytoin, a poorly soluble antiepileptic API (solubility ~ 80 µmole/L), was obtained from SCF engineered nanosized phenytoin. Nanosized prednisolone (mean size of 230 nm), a model API **with** low **solubility** in both water and CO_2, was engineered using SCF technology. Prednisolone was dissolved in an organic solvent in the presence a hydrophilic polymer and a surfactant, after which the solution was sprayed into a supercritical CO_2 [176]. Nanosized apigenin prepared by the SCF antisolvent process showed enhanced dissolution profiles at different pH values in comparison to parent particles [177]. Other examples include the use of SCF technology to enhance the dissolution rate of tetracycline [178], griseofulvin [127], ibuprofen [125], cyclosporine [179], paclitaxel [180] and theophylline [181] (Tables 3 and 7). The SCF technology has been also used to engineer nanosized APIs with improved stability. For example, SCF technology was used to transform an amorphous salbutamol sulphate to a crystalline form to improve its stability and aerosolization performance from DPIs [276].

Table 7. Scanning electron microscopy (SEM) photographs of some nanosized APIs prepared using supercritical fluid (SCF) technology in comparison to their parent raw materials.

API	Raw material	Nanosized material	SCF technique	Reference
Phenytoin			RESS-SC	[175]
Apigenin			SAS	[177]
Griseofulvin			SAS	[127]
Theophylline			RESS-SC	[181]

7. Disadvantages of nanosized delivery systems

Nanosuspensions are thermodynamically metastable dispersions and, therefore, their stability is a critical issue [213]. The stabilization of nanosuspensions could be achieved by adding surfactants, which could be charged amphiphiles or non-ionic polymers. The charged amphiphiles include bile salts (e.g., sodium cholate) and alkyl sulfonates (e.g., SDS, sodium dioctylsulfosuccinate and SLS), and they work by electrostatic stabilization, whereas non-ionic polymers (e.g., polysorbates, poloxamines and poloxamers) work by a different mechanism. The attachment of the hydrophobic domain of non-ionic polymers of the surfactants creates a hydrophobic domain to the surface, which provides a surface affinity that inhibits aggregation. Another factor is the layer of hydration that is created by attachment of the hydrophobic domain to the particle surface. This layer of hydration needs a work to be removed in order for aggregation to be feasible and thus aggregation is inhibited. Furthermore, the hydrophilic moieties of surfactants prevent aggregation [213,277]. The API leaking and the uneven API distribution are commonly encountered problems with nanoparticles prepared by emulsion [257].

Particle reduction of APIs into a nanosized range remains challenging due to the aggregation of the high surface area nanosized particles [27]. In the context of pulmonary API delivery, such aggregation results in a low emitted dose of the nanosized API upon inhalation, poor flow properties, and extreme powder handling difficulties [91]. DPIs containing nanoparticle powder formulations have a major drawback, which is their aerodynamic diameter being unsuitable for good inhalation delivery [278–280]. This leads to a low API delivery efficiency due to a large fraction of the inhaled dose being exhaled. The low API loading efficiency and the difficulties associated with scaling the process up are also limitations of the nanosized pulmonary delivery systems. Additionally, there are few safety concerns related to the long-term inhalation of stabilizers used during the preparation of nanocrystals. It is also very important to control the residual solvents and cytotoxic excipients [93] and the potential adverse effects of nanoparticles on pulmonary structure and function [281].

8. Conclusions and outlook

Different techniques to produce nanosized APIs were reviewed with emphasis on the merits, the limitations and the applications related to each method. The existing production technologies of

nanosized APIs are mainly classified into bottom-up techniques, top-down techniques, and a combination of both.

Nanoparticle engineering is a promising tool to resolve many current issues associated with poorly soluble APIs, such as those related to poor solubility and dissolution rate. Converting nanosuspensions into solid dosage forms can solve many problems associated with API development such as poor bioavailability. However, the industrial scale production of nanosized systems is still a challenge. This is, in part, because most of the technologies that have been utilized to enhance the dissolution rate of poorly soluble APIs via the nanosizing route produce amorphous systems, which are metastable and possess tremendous challenges during processing, making them unfavourable in the pharmaceutical industry. Additionally, serious challenges could be associated with the preparation of nanosized APIs, such as separating the nanosized APIs from surfactants, low formulation yield, contamination with microsized particles, and those related to the ability to re-suspend the nanosized APIs after drying. Therefore, there is an increased need for innovative nanosizing technologies that can produce crystalline APIs with both high stability profiles and enhanced dissolution rates. The optimization of nanosizing processes using Quality by Design methods might open new horizons in the development of nanosized pharmaceutical formulations.

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References

[1] Mohanraj VJ, Chen Y. Nanoparticles-a review. Trop J Pharm Res 2007;5:561–73.

[2] Kreuter J. Nanoparticles-a historical perspective. Int J Pharm 2007;331:1–10.

[3] Sung JC, Pulliam BL, Edwards D a. Nanoparticles for drug delivery to the lungs. Trends Biotechnol 2007;25:563–70. doi:10.1016/j.tibtech.2007.09.005.

[4] Brannon-Peppas L, Blanchette JO. Nanoparticle and targeted systems for cancer therapy. Adv Drug Deliv Rev 2004;64:206–12. doi:10.1016/j.addr.2012.09.033.

[5] Pandey R, Sharma S, Khuller GK. Oral solid lipid nanoparticle-based antitubercular chemotherapy. Tuberculosis 2005;85:415–20. doi:10.1016/j.tube.2005.08.009.

[6] Gelperina S, Kisich K, Iseman MD, Heifets L. The potential advantages of nanoparticle drug delivery systems in chemotherapy of tuberculosis. Am J Respir Crit Care Med 2005;172:1487–90. doi:10.1164/rccm.200504-613PP.

[7] Chen H, Khemtong C, Yang X, Chang X, Gao J. Nanonization strategies for poorly water-soluble drugs. Drug Discov Today 2011;16:354–60. doi:10.1016/j.drudis.2010.02.009.

[8] Lipinski C a. Poor Aqueous Solubility-an Industry Wide Problem in ADME Screening. Am Pharm Rev 2002;5:82–5.

[9] Kang J, Kumar V, Yang D, Chowdhury PR, Hohl RJ. Cyclodextrin complexation: Influence on the solubility, stability, and cytotoxicity of camptothecin, an antineoplastic agent. Eur J Pharm Sci 2002;15:163–70. doi:10.1016/S0928-0987(01)00214-7.

[10] Zhou Z, D'Emanuele A, Attwood D. Solubility enhancement of paclitaxel using a linear-dendritic block copolymer. Int J Pharm 2013;452:173–9. doi:10.1016/j.ijpharm.2013.04.075.

[11] Serajuddin a. TM. Salt formation to improve drug solubility. Adv Drug Deliv Rev 2007;59:603–16. doi:10.1016/j.addr.2007.05.010.

[12] Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today 2007;12:1068–75. doi:10.1016/j.drudis.2007.09.005.

[13] Cerpnjak K, Zvonar A, Gašperlin M, Vrečer F. Lipid-based systems as a promising approach for enhancing the bioavailability of poorly water-soluble drugs. Acta Pharm 2013;63:427–45. doi:10.2478/acph-2013-0040.

[14] Merisko-Liversidge EM, Liversidge GG. Drug nanoparticles: formulating poorly water-soluble compounds. Toxicol Pathol 2008;36:43–8. doi:10.1177/0192623307310946.

[15] A. Noyes WW. The rate of solution of solid substances in their own Solutions. J Am Chem Soc 1897;19:pp. 930–4.

[16] W. Nernst. Theorie der Reaktionsgeschwindigkeit in heterogenen Systemen. Z Phys Chem 1904;47:52–5.

[17] Brunner E. Reaktionsgeschwindigkeit in heterogenen Systemen. Z Phys Chem 1904;47:56–102.

[18] Dressman JB, Amidon GL, Reppas C SV. Dissolution testing as a prognostic tool for oral drug adsorption. Pharm Res 1998;15:11–22.

[19] Dokoumetzidis A, Macheras P. A century of dissolution research: From Noyes and Whitney to the Biopharmaceutics Classification System. Int J Pharm 2006;321:1–11. doi:10.1016/j.ijpharm.2006.07.011.

[20] Wu Y, Loper A, Landis E, Hettrick L, Novak L, Lynn K, et al. The role of

biopharmaceutics in the development of a clinical nanoparticle formulation of MK-0869: A Beagle dog model predicts improved bioavailability and diminished food effect on absorption in human. Int J Pharm 2004;285:135–46. doi:10.1016/j.ijpharm.2004.08.001.

[21] Miao X, Sun C, Jiang T, Zheng L, Wang T WS. Investigation of nanosized crystalline form to improve the oral bioavailability of poorly water soluble cilostazol. J Pharm Pharm Sci 2011;14(2):196–214.

[22] C Nyström MB. Physiochemical aspects of drug release. VIII. The relation between particle size and surface specific dissolution rate in agitated suspensions. Int J Pharm 1988;47:223–31No.

[23] Freundlich H. Colloid and Capillary Chemistry, New York. E. P. Dutton and Company; 1923.

[24] W. Ostwald. Z. Phys. Chem. vol. 34. 1900.

[25] Müller RH, Peters K. Nanosuspensions for the formulation of poorly soluble drugs. Int J Pharm 1998;160:229–37. doi:10.1016/S0378-5173(97)00311-6.

[26] Ganta S, Paxton JW, Baguley BC, Garg S. Formulation and pharmacokinetic evaluation of an asulacrine nanocrystalline suspension for intravenous delivery. Int J Pharm 2009;367:179–86. doi:10.1016/j.ijpharm.2008.09.022.

[27] Merisko-Liversidge E, Liversidge GG, Cooper ER. Nanosizing: A formulation approach for poorly-water-soluble compounds. Eur J Pharm Sci 2003;18:113–20. doi:10.1016/S0928-0987(02)00251-8.

[28] Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Deliv Rev 2007;59:617–30. doi:10.1016/j.addr.2007.05.011.

[29] Müller RH, Jacobs C, Kayser O. Nanosuspensions as particulate drug formulations in therapy: Rationale for development and what we can expect for the future. Adv Drug Deliv Rev 2001;47:3–19. doi:10.1016/S0169-409X(00)00118-6.

[30] Hecq J, Deleers M, Fanara D, Vranckx H, Amighi K. Preparation and characterization of nanocrystals for solubility and dissolution rate enhancement of nifedipine. Int J Pharm 2005;299:167–77. doi:10.1016/j.ijpharm.2005.05.014.

[31] Horn D, Rieger J. Organic nanoparticles in aqueous phase. Angew Chem Int Ed Engl 2001;40:4330–61.

[32] Hanafy a., Spahn-Langguth H, Vergnault G, Grenier P, Tubic Grozdanis M, Lenhardt T, et al. Pharmacokinetic evaluation of oral fenofibrate nanosuspensions and SLN in comparison to conventional suspensions of micronized drug. Adv Drug Deliv Rev 2007;59:419–26. doi:10.1016/j.addr.2007.04.005.

[33] Jinno JI, Kamada N, Miyake M, Yamada K, Mukai T, Odomi M, et al. Effect of particle size reduction on dissolution and oral absorption of a poorly water-soluble drug, cilostazol, in beagle dogs. J Control Release 2006;111:56–64. doi:10.1016/j.jconrel.2005.11.013.

[34] Kocbek P, Baumgartner S, Kristl J. Preparation and evaluation of nanosuspensions for enhancing the dissolution of poorly soluble drugs. Int J Pharm 2006;312:179–86. doi:10.1016/j.ijpharm.2006.01.008.

[35] Pace, Sarah N. et al. Novel injectable formulations of insoluble drugs. Pharm Technol 233 1999:116–34.

[36] Kesisoglou F, Mitra A. Crystalline Nanosuspensions as Potential Toxicology and Clinical

Oral Formulations for BCS II/IV Compounds. AAPS J 2012;14:677–87. doi:10.1208/s12248-012-9383-0.
[37] Ghosh I, Bose S, Vippagunta R, Harmon F. Nanosuspension for improving the bioavailability of a poorly soluble drug and screening of stabilizing agents to inhibit crystal growth. Int J Pharm 2011;409:260–8.
[38] Constantinides PP, Chaubal M V, Shorr R. Advances in lipid nanodispersions for parenteral drug delivery and targeting. Adv Drug Deliv Rev 2008;60:757–67.
[39] Van Eerdenbrugh B, Van den Mooter G, Augustijns P. Top-down production of drug nanocrystals: nanosuspension stabilization, miniaturization and transformation into solid products. Int J Pharm 2008;364:64–75.
[40] Alexis F, Pridgen E, Molnar LK, Farokhzad OC. Factors affecting the clearance and biodistribution of polymeric nanoparticles. Mol Pharm 2008;5:505–15.
[41] Kesisoglou F, Panmai S WYN. Nanosizing—oral formulation development and biopharmaceutical evaluation. Adv Drug Deliv Rev 2007;59:631–44.
[42] Barbe C, Bartlett J, Kong L, Finnie K, Lin HQ, Larkin M, et al. Silica particles: a novel drug-delivery system. Adv Mater 2004;16:1959–66.
[43] Jaganathan H, Godin B. Biocompatibility assessment of Si-based nano-and micro-particles. Adv Drug Deliv Rev 2012;64:1800–19.
[44] Dhumal RS, Biradar S V., Paradkar AR, York P. Particle engineering using sonocrystallization: Salbutamol sulphate for pulmonary delivery. Int J Pharm 2009;368:129–37. doi:10.1016/j.ijpharm.2008.10.006.
[45] Giri S, Trewyn BG, Lin VSY. Mesoporous silica nanomaterial-based biotechnological and biomedical delivery systems 2007.
[46] Yang P, Gai S, Lin J. Functionalized mesoporous silica materials for controlled drug delivery. Chem Soc Rev 2012;41:3679–98.
[47] Zhang Z, Wang L, Wang J, Jiang X, Li X, Hu Z, et al. Mesoporous Silica-Coated Gold Nanorods as a Light-Mediated Multifunctional Theranostic Platform for Cancer Treatment. Adv Mater 2012;24:1418–23.
[48] Wilding I, Hirst P, Connor A. Development of a new engineering-based capsule for human drug absorption studies. Pharm Sci Technolo Today 2000;3:385–92.
[49] Sugano K. Possible reduction of effective thickness of intestinal unstirred water layer by particle drifting effect. Int J Pharm 2010;387:103–9. doi:10.1016/j.ijpharm.2009.12.014.
[50] Juenemann D, Jantratid E, Wagner C, Reppas C, Vertzoni M, Dressman JB. Biorelevant in vitro dissolution testing of products containing micronized or nanosized fenofibrate with a view to predicting plasma profiles. Eur J Pharm Biopharm 2011;77:257–64. doi:10.1016/j.ejpb.2010.10.012.
[51] Jinno JI, Kamada N, Miyake M, Yamada K, Mukai T, Odomi M, et al. In vitro-in vivo correlation for wet-milled tablet of poorly water-soluble cilostazol. J Control Release 2008;130:29–37. doi:10.1016/j.jconrel.2008.05.013.
[52] Gao L, Liu G, Kang J, Niu M, Wang Z, Wang H, et al. Paclitaxel nanosuspensions coated with P-gp inhibitory surfactants: I. Acute toxicity and pharmacokinetics studies. Colloids Surfaces B Biointerfaces 2013;111:277–81. doi:10.1016/j.colsurfb.2013.06.004.
[53] Mauludin R, Müller RH, Keck CM. Development of an oral rutin nanocrystal formulation. Int J Pharm 2009;370:202–9. doi:10.1016/j.ijpharm.2008.11.029.

[54] Rao et al. Formulation of Nanosuspensions of Albendazole for Oral Administration. Curr Nanosci 2008;4:53–8.
[55] Zhang D, Tan T, Gao L, Zhao W, Wang P. Preparation of azithromycin nanosuspensions by high pressure homogenization and its physicochemical characteristics studies. Drug Dev Ind Pharm 2007;33:569–75. doi:10.1080/03639040600975147.
[56] Gao L, Zhang D, Chen M, Duan C, Dai W, Jia L, et al. Studies on pharmacokinetics and tissue distribution of oridonin nanosuspensions. Int J Pharm 2008;355:321–7. doi:10.1016/j.ijpharm.2007.12.016.
[57] Teeranachaideekul V, Junyaprasert VB, Souto EB, Müller RH. Development of ascorbyl palmitate nanocrystals applying the nanosuspension technology. Int J Pharm 2008;354:227–34. doi:10.1016/j.ijpharm.2007.11.062.
[58] Liversidge, Gary G., Christopher P. Phillips and KCC. Method to reduce particle size growth during lyophilization, 1994.
[59] Bernard VE, Sofie V, a.M.J. MJ, Jan V, Ludo F, Jan VH, et al. Microcrystalline cellulose, a useful alternative for sucrose as a matrix former during freeze-drying of drug nanosuspensions - A case study with itraconazole. Eur J Pharm Biopharm 2008;70:590–6. doi:10.1016/j.ejpb.2008.06.007.
[60] Ain-Ai A, Gupta PK. Effect of arginine hydrochloride and hydroxypropyl cellulose as stabilizers on the physical stability of high drug loading nanosuspensions of a poorly soluble compound. Int J Pharm 2008;351:282–8. doi:10.1016/j.ijpharm.2007.09.029.
[61] Van Eerdenbrugh B, Froyen L, Van Humbeeck J, Martens J a., Augustijns P, Van den Mooter G. Drying of crystalline drug nanosuspensions-The importance of surface hydrophobicity on dissolution behavior upon redispersion. Eur J Pharm Sci 2008;35:127–35. doi:10.1016/j.ejps.2008.06.009.
[62] Guo M, Fu Q, Wu C, Guo Z, Li M, Sun J, et al. Rod shaped nanocrystals exhibit superior in vitro dissolution and in vivo bioavailability over spherical like nanocrystals: A case study of lovastatin. Colloids Surfaces B Biointerfaces 2015;128:410–8. doi:10.1016/j.colsurfb.2015.02.039.
[63] Chaubal M V., Popescu C. Conversion of nanosuspensions into dry powders by spray drying: A case study. Pharm Res 2008;25:2302–8. doi:10.1007/s11095-008-9625-0.
[64] Hu J, Ng WK, Dong Y, Shen S, Tan RBH. Continuous and scalable process for water-redispersible nanoformulation of poorly aqueous soluble APIs by antisolvent precipitation and spray-drying. Int J Pharm 2011;404:198–204. doi:10.1016/j.ijpharm.2010.10.055.
[65] Dolenc A, Kristl J, Baumgartner S, Planinšek O. Advantages of celecoxib nanosuspension formulation and transformation into tablets. Int J Pharm 2009;376:204–12. doi:10.1016/j.ijpharm.2009.04.038.
[66] Van Eerdenbrugh B, Froyen L, Van Humbeeck J, Martens J a., Augustijns P, Van Den Mooter G. Alternative matrix formers for nanosuspension solidification: Dissolution performance and X-ray microanalysis as an evaluation tool for powder dispersion. Eur J Pharm Sci 2008;35:344–53. doi:10.1016/j.ejps.2008.08.003.
[67] Chiou H, Li L, Hu T, Chan HK, Chen JF, Yun J. Production of salbutamol sulfate for inhalation by high-gravity controlled antisolvent precipitation. Int J Pharm 2007;331:93–8. doi:10.1016/j.ijpharm.2006.09.022.
[68] Kim S, Lee J. Effective polymeric dispersants for vacuum, convection and freeze drying of drug nanosuspensions. Int J Pharm 2010;397:218–24. doi:10.1016/j.ijpharm.2010.07.010.

[69] Kakran M, Sahoo NG, Li L, Judeh Z, Wang Y, Chong K, et al. Fabrication of drug nanoparticles by evaporative precipitation of nanosuspension. Int J Pharm 2010;383:285–92. doi:10.1016/j.ijpharm.2009.09.030.

[70] Gao L, Liu G, Wang X, Liu F, Xu Y, Ma J. Preparation of a chemically stable quercetin formulation using nanosuspension technology. Int J Pharm 2011;404:231–7. doi:10.1016/j.ijpharm.2010.11.009.

[71] Ahmed A. Hussein and Hasanain Sh. Mahmood. Preparation and evaluation of 2014;23. doi:10.1007/s11274-013-1314-4.

[72] Wickström H, Palo M, Rijckaert K, Kolakovic R, Nyman JO, Määttänen A, et al. Improvement of dissolution rate of indomethacin by inkjet printing. Eur J Pharm Sci 2015;75:91–100. doi:10.1016/j.ejps.2015.03.009.

[73] Bhakay A, Davé R, Bilgili E. Recovery of BCS Class II drugs during aqueous redispersion of core-shell type nanocomposite particles produced via fluidized bed coating. Powder Technol 2013;236:221–34. doi:10.1016/j.powtec.2011.12.066.

[74] Basa S, Muniyappan T, Karatgi P, Prabhu R, Pillai R. Production and in vitro characterization of solid dosage form incorporating drug nanoparticles. Drug Dev Ind Pharm 2008;34:1209–18. doi:10.1080/03639040802005024.

[75] Kayaert P, Anné M, Van Den Mooter G. Bead layering as a process to stabilize nanosuspensions: Influence of drug hydrophobicity on nanocrystal reagglomeration following in-vitro release from sugar beads. J Pharm Pharmacol 2011;63:1446–53. doi:10.1111/j.2042-7158.2011.01351.x.

[76] Bhakay A, Azad M, Bilgili E, Dave R. Redispersible fast dissolving nanocomposite microparticles of poorly water-soluble drugs. Int J Pharm 2014;461:367–79. doi:10.1016/j.ijpharm.2013.11.059.

[77] Sinha B, Müller RH, Möschwitzer JP. Bottom-up approaches for preparing drug nanocrystals: Formulations and factors affecting particle size. Int J Pharm 2013;453:126–41. doi:10.1016/j.ijpharm.2013.01.019.

[78] de Waard H, Hinrichs WLJ, Frijlink HW. A novel bottom-up process to produce drug nanocrystals: Controlled crystallization during freeze-drying. J Control Release 2008;128:179–83. doi:10.1016/j.jconrel.2008.03.002.

[79] Badawi A a, El-Nabarawi MA, El-Setouhy DA, Alsammit SA. Formulation and stability testing of itraconazole crystalline nanoparticles. AAPS PharmSciTech 2011;12:811–20. doi:10.1208/s12249-011-9651-9.

[80] de Paiva Lacerda S, Espitalier F, Hoffart V, Ré MI. Liquid anti-solvent recrystallization to enhance dissolution of CRS 74, a new antiretroviral drug. Drug Dev Ind Pharm 2015;9045:1–11. doi:10.3109/03639045.2015.1020812.

[81] Schmidt C, Bodmeier R. Incorporation of polymeric nanoparticles into solid dosage forms. J Control Release 1999;57:115–25.

[82] Liversidge GG, Cundy KC. Particle size reduction for improvement of oral bioavailability of hydrophobic drugs: I. Absolute oral bioavailability of nanocrystalline danazol in beagle dogs. Int J Pharm 1995;125:91–7. doi:10.1016/0378-5173(95)00122-Y.

[83] Goole J, Lindley DJ, Roth W, Carl SM, Amighi K, Kauffmann JM, et al. The effects of excipients on transporter mediated absorption. Int J Pharm 2010;393:17–31. doi:10.1016/j.ijpharm.2010.04.019.

[84] Van Eerdenbrugh B, Van den Mooter G, Augustijns P. Top-down production of drug nanocrystals: Nanosuspension stabilization, miniaturization and transformation into solid

products. Int J Pharm 2008;364:64–75. doi:10.1016/j.ijpharm.2008.07.023.
[85] Jang et al. Novel nanocrystal formulation of megestrol acetate has improved bioavailability compared with the conventional micronized formulation in the fasting state. Drug Des Devel Ther 2014;8:851–8.
[86] Leone F, Cavalli R. Drug nanosuspensions : a ZIP tool between traditional and innovative pharmaceutical formulations 2015:1–19. doi:10.1517/17425247.2015.1043886.
[87] Vergote GJ, Vervaet C, Van Driessche I, Hoste S, De Smedt S, Demeester J, et al. An oral controlled release matrix pellet formulation containing nanocrystalline ketoprofen. Int J Pharm 2001;219:81–7. doi:10.1016/S0378-5173(01)00628-7.
[88] Rogueda PGA, Traini D. The nanoscale in pulmonary delivery. Part 1: deposition, fate, toxicology and effects 2007.
[89] Rogueda PGA, Traini D. The nanoscale in pulmonary delivery. Part 2: formulation platforms 2007.
[90] Yang W, Peters JI, Williams RO. Inhaled nanoparticles-A current review. Int J Pharm 2008;356:239–47. doi:10.1016/j.ijpharm.2008.02.011.
[91] Hadinoto K, Phanapavudhikul P, Kewu Z, Tan RBH. Dry powder aerosol delivery of large hollow nanoparticulate aggregates as prospective carriers of nanoparticulate drugs: effects of phospholipids. Int J Pharm 2007;333:187–98.
[92] Pison U, Welte T, Giersig M, Groneberg DA. Nanomedicine for respiratory diseases. Eur J Pharmacol 2006;533:341–50.
[93] Bailey MM, Berkland CJ. Nanoparticle formulations in pulmonary drug delivery. Med Res Rev 2009;29:196–212.
[94] Salem H, Abdelrahim M, Eid KA, Sharaf M. Nanosized rods agglomerates as a new approach for formulation of a dry powder inhaler. Int J Nanomedicine 2011;6:311–20. doi:10.2147/IJN.S14309.
[95] Tsapis N, Bennett D, Jackson B, Weitz D a, Edwards D a. Trojan particles: large porous carriers of nanoparticles for drug delivery. Proc Natl Acad Sci U S A 2002;99:12001–5. doi:10.1073/pnas.182233999.
[96] Sham JOH, Zhang Y, Finlay WH, Roa WH, Löbenberg R. Formulation and characterization of spray-dried powders containing nanoparticles for aerosol delivery to the lung. Int J Pharm 2004;269:457–67. doi:10.1016/j.ijpharm.2003.09.041.
[97] Grenha A, Seijo B, Remuñán-López C. Microencapsulated chitosan nanoparticles for lung protein delivery. Eur J Pharm Sci 2005;25:427–37. doi:10.1016/j.ejps.2005.04.009.
[98] Hadinoto K, Phanapavudhikul P, Kewu Z, Tan RBH. Novel formulation of large hollow nanoparticles aggregates as potential carriers in inhaled delivery of nanoparticulate drugs. Ind Eng Chem Res 2006;45:3697–706.
[99] Bailey MM, Gorman EM, Munson EJ, Berkland C. Pure insulin nanoparticle agglomerates for pulmonary delivery. Langmuir 2008;24:13614–20. doi:10.1021/la802405p.
[100] El-Gendy N, Berkland C. Combination chemotherapeutic dry powder aerosols via controlled nanoparticle agglomeration. Pharm Res 2009;26:1752–63. doi:10.1007/s11095-009-9886-2.
[101] Plumley C, Gorman EM, El-Gendy N, Bybee CR, Munson EJ, Berkland C. Nifedipine nanoparticle agglomeration as a dry powder aerosol formulation strategy. Int J Pharm 2009;369:136–43. doi:10.1016/j.ijpharm.2008.10.016.
[102] Vaughn JM, McConville JT, Burgess D, Peters JI, Johnston KP, Talbert RL, et al. Single

dose and multiple dose studies of itraconazole nanoparticles. Eur J Pharm Biopharm 2006;63:95–102.
[103] Huber G, Wirth K-E. Electrostatically supported surface coating of solid particles in liquid nitrogen for use in dry-powder-inhalers. Powder Technol 2003;134:181–92.
[104] Mykhaylova V. Development of microparticle-nanoparticle powder mixtures for the use in dry powder inhalers 2009.
[105] Beck-Broichsitter M, Schweiger C, Schmehl T, Gessler T, Seeger W, Kissel T. Characterization of novel spray-dried polymeric particles for controlled pulmonary drug delivery. J Control Release 2012;158:329–35. doi:10.1016/j.jconrel.2011.10.030.
[106] Panyam J, Labhasetwar V. Biodegradable nanoparticles for drug and gene delivery to cells and tissue. Adv Drug Deliv Rev 2003;55:329–47.
[107] Kawashima Y, Yamamoto H, Takeuchi H, Hino T, Niwa T. Properties of a peptide containing DL-lactide/glycolide copolymer nanospheres prepared by novel emulsion solvent diffusion methods. Eur J Pharm Biopharm 1998;45:41–8. doi:10.1016/S0939-6411(97)00121-5.
[108] Zhang Q, Shen Z, Nagai T. Prolonged hypoglycemic effect of insulin-loaded polybutylcyanoacrylate nanoparticles after pulmonary administration to normal rats. Int J Pharm 2001;218:75–80. doi:10.1016/S0378-5173(01)00614-7.
[109] Yamamoto H, Kuno Y, Sugimoto S, Takeuchi H, Kawashima Y. Surface-modified PLGA nanosphere with chitosan improved pulmonary delivery of calcitonin by mucoadhesion and opening of the intercellular tight junctions. J Control Release 2005;102:373–81.
[110] Zahoor A, Sharma S, Khuller GK. Inhalable alginate nanoparticles as antitubercular drug carriers against experimental tuberculosis. Int J Antimicrob Agents 2005;26:298–303.
[111] Sharma A, Sharma S, Khuller GK. Lectin-functionalized poly (lactide-co-glycolide) nanoparticles as oral/aerosolized antitubercular drug carriers for treatment of tuberculosis. J Antimicrob Chemother 2004;54:761–6.
[112] Ong HX, Traini D, Cipolla D, Gonda I, Bebawy M, Agus H, et al. Liposomal nanoparticles control the uptake of ciprofloxacin across respiratory epithelia. Pharm Res 2012;29:3335–46.
[113] Lindfors L, Skantze P, Skantze U, Westergren J, Olsson U. Amorphous drug nanosuspensions. 3. Particle dissolution and crystal growth. Langmuir 2007;23:9866–74. doi:10.1021/la700811b.
[114] Jiang T, Han N, Zhao B, Xie Y, Wang S. Enhanced dissolution rate and oral bioavailability of simvastatin nanocrystal prepared by sonoprecipitation. Drug Dev Ind Pharm 2012;38:1230–9. doi:10.3109/03639045.2011.645830.
[115] Ige PP, Baria RK, Gattani SG. Fabrication of fenofibrate nanocrystals by probe sonication method for enhancement of dissolution rate and oral bioavailability. Colloids Surfaces B Biointerfaces 2013;108:366–73. doi:10.1016/j.colsurfb.2013.02.043.
[116] Zhang J, Lv H, Jiang K, Gao Y. Enhanced bioavailability after oral and pulmonary administration of baicalein nanocrystal. Int J Pharm 2011;420:180–8. doi:10.1016/j.ijpharm.2011.08.023.
[117] Sahu BP, Das MK. Preparation and in vitro/in vivo evaluation of felodipine nanosuspension. Eur J Drug Metab Pharmacokinet 2013:1–11. doi:10.1007/s13318-013-0158-5.
[118] Mou D, Chen H, Wan J, Xu H, Yang X. Potent dried drug nanosuspensions for oral bioavailability enhancement of poorly soluble drugs with pH-dependent solubility. Int J

Pharm 2011;413:237–44. doi:10.1016/j.ijpharm.2011.04.034.
[119] El-gendy et al. Budesonide Nanoparticle Agglomerates as Dry Powder Aerosols With Rapid Dissolution. Wiley Intersci 2009.
[120] Hou C-D, Wang J-X, Le Y, Zou H-K, Zhao H. Preparation of azithromycin nanosuspensions by reactive precipitation method. Drug Dev Ind Pharm 2012;38:848–54. doi:10.3109/03639045.2011.630394.
[121] Zhao H, Wang J, Zhang H, Shen Z, Yun J, Chen J. Facile Preparation of Danazol Nanoparticles by High-Gravity Anti-solvent Precipitation (HGAP) Method. Chinese J Chem Eng 2009;17:318–23. doi:10.1016/S1004-9541(08)60210-4.
[122] Chen JF, Zhang JY, Shen ZG, Zhong J, Yun J. Preparation and characterization of amorphous cefuroxime axetil drug nanoparticles with novel technology: High-gravity antisolvent precipitation. Ind Eng Chem Res 2006;45:8723–7. doi:10.1021/ie060445h.
[123] Wang Z, Chen JF, Le Y, Shen ZG, Yun J. Preparation of ultrafine beclomethasone dipropionate drug powder by antisolvent precipitation. Ind Eng Chem Res 2007;46:4839–45. doi:10.1021/ie0615537.
[124] Zhong J, Shen Z, Yang Y, Chen J. Preparation and characterization of uniform nanosized cephradine by combination of reactive precipitation and liquid anti-solvent precipitation under high gravity environment. Int J Pharm 2005;301:286–93. doi:10.1016/j.ijpharm.2005.06.005.
[125] Pathak P, Meziani MJ, Desai T, Sun YP. Formation and stabilization of ibuprofen nanoparticles in supercritical fluid processing. J Supercrit Fluids 2006;37:279–86. doi:10.1016/j.supflu.2005.09.005.
[126] Yasuji T, Takeuchi H, Kawashima Y. Particle design of poorly water-soluble drug substances using supercritical fluid technologies. Adv Drug Deliv Rev 2008;60:388–98. doi:10.1016/j.addr.2007.03.025.
[127] Chattopadhyay P, Gupta RB. Production of griseofulvin nanoparticles using supercritical CO2 antisolvent with enhanced mass transfer. Int J Pharm 2001;228:19–31. doi:10.1016/S0378-5173(01)00803-1.
[128] Reverchon E, De Marco I, Della Porta G. Tailoring of nano- and micro-particles of some superconductor precursors by supercritical antisolvent precipitation. J Supercrit Fluids 2002;23:81–7. doi:10.1016/S0896-8446(01)00129-2.
[129] Hu TT, Wang JX, Shen ZG, Chen JF. Engineering of drug nanoparticles by HGCP for pharmaceutical applications. Particuology 2008;6:239–51. doi:10.1016/j.partic.2008.04.001.
[130] Pu X, Sun J, Wang Y, Wang Y, Liu X, Zhang P, et al. Development of a chemically stable 10-hydroxycamptothecin nanosuspensions. Int J Pharm 2009;379:167–73. doi:10.1016/j.ijpharm.2009.05.062.
[131] Müller RH, Jacobs C. Buparvaquone mucoadhesive nanosuspension: Preparation, optimisation and long-term stability. Int J Pharm 2002;237:151–61. doi:10.1016/S0378-5173(02)00040-6.
[132] Möschwitzer J, Achleitner G, Pomper H, Müller RH. Development of an intravenously injectable chemically stable aqueous omeprazole formulation using nanosuspension technology. Eur J Pharm Biopharm 2004;58:615–9. doi:10.1016/j.ejpb.2004.03.022.
[133] Hong C, Dang Y, Lin G, Yao Y, Li G, Ji G, et al. Effects of stabilizing agents on the development of myricetin nanosuspension and its characterization: An in vitro and in vivo evaluation. Int J Pharm 2014;477:251–60. doi:10.1016/j.ijpharm.2014.10.044.

[134] Rabinow B, Kipp J, Papadopoulos P, Wong J, Glosson J, Gass J, et al. Itraconazole IV nanosuspension enhances efficacy through altered pharmacokinetics in the rat. Int J Pharm 2007;339:251–60. doi:10.1016/j.ijpharm.2007.02.030.
[135] Donsí F, Wang Y, Li JI, Huang Q. Preparation of curcumin sub-micrometer dispersions by high-pressure homogenization. J Agric Food Chem 2010;58:2848–53. doi:10.1021/jf903968x.
[136] Li W, Yang Y, Tian Y, Xu X, Chen Y, Mu L, et al. Preparation and in vitro/in vivo evaluation of revaprazan hydrochloride nanosuspension. Int J Pharm 2011;408:157–62. doi:10.1016/j.ijpharm.2011.01.059.
[137] Fu Q, Sun J, Zhang D, Li M, Wang Y, Ling G, et al. Nimodipine nanocrystals for oral bioavailability improvement: Preparation, characterization and pharmacokinetic studies. Colloids Surfaces B Biointerfaces 2013;109:161–6. doi:10.1016/j.colsurfb.2013.01.066.
[138] Kayser O, Olbrich C, Yardley V, Kiderlen a. F, Croft SL. Formulation of amphotericin B as nanosuspension for oral administration. Int J Pharm 2003;254:73–5. doi:10.1016/S0378-5173(02)00686-5.
[139] Schöler N, Krause K, Kayser O, Rainer H, Borner K, Hahn H, et al. Atovaquone Nanosuspensions Show Excellent Therapeutic Effect in a New Murine Model of Reactivated Toxoplasmosis Atovaquone Nanosuspensions Show Excellent Therapeutic Effect in a New Murine Model of Reactivated Toxoplasmosis 2001;45:1771–9. doi:10.1128/AAC.45.6.1771.
[140] Liversidge GG, Conzentino P. Drug particle size reduction for decreasing gastric irritancy and enhancing absorption of naproxen in rats. Int J Pharm 1995;125:309–13. doi:10.1016/0378-5173(95)00148-C.
[141] Onoue S, TAKAHASHI H, KAWABATA Y, SETO Y, HATANAKA J, TIMMERMANN B, et al. Formulation Design and Photochemical Studies on Nanocrystal Solid Dispersion of Curcumin With Improved Oral Bioavailability. Wiley Intersci 2009.
[142] Merisko-Liversidge E, McGurk SL, Liversidge GG. Insulin nanoparticles: A novel formulation approach for poorly water soluble Zn-insulin. Pharm Res 2004;21:1545–53. doi:10.1023/B:PHAM.0000041446.14569.e2.
[143] De Smet L, Saerens L, De Beer T, Carleer R, Adriaensens P, Van Bocxlaer J, et al. Formulation of itraconazole nanococrystals and evaluation of their bioavailability in dogs. Eur J Pharm Biopharm 2014;87:107–13. doi:10.1016/j.ejpb.2013.12.016.
[144] Choi JY, Yoo JY, Kwak HS, Nam BU, Lee J. Role of polymeric stabilizers for drug nanocrystal dispersions. Curr Appl Phys 2005;5:472–4. doi:10.1016/j.cap.2005.01.012.
[145] Pentecost A, Gour S, Mochalin V, Knoke I, Gogotsi Y. Deaggregation of nanodiamond powders using salt- and sugar-assisted milling. ACS Appl Mater Interfaces 2010;2:3289–94. doi:10.1021/am100720n.
[146] Mochalin VN, Sagar A, Gour S, Gogotsi Y. Manufacturing nanosized fenofibrate by salt assisted milling. Pharm Res 2009;26:1365–70. doi:10.1007/s11095-009-9846-x.
[147] Wongmekiat A, Yoshimatsu S, Tozuka Y, Moribe K, Yamamoto K. Investigation of drug nanoparticle formation by co-grinding with cyclodextrins: studies for indomethacin, furosemide and naproxen. J Incl Phenom Macrocycl Chem 2006;56:29–32.
[148] Tozuka Y, Wongmekiat A, Sakata K, Moribe K, Oguchi T, Yamamoto K. Co-grinding with cyclodextrin as a nanoparticle preparation method of a poorly water soluble drug. J Incl Phenom Macrocycl Chem 2004;50:67–71.
[149] Yamada T, SAITO N, Imai T, OTAGIRI M. Effect of grinding with hydroxypropyl

cellulose on the dissolution and particle size of a poorly water-soluble drug. Chem Pharm Bull 1999;47:1311–3.
[150] Limwikrant W, Osada M, Higashi K, Tozuka Y, Moribe K, Yamamoto K. Unique indomethacin nanoparticles formation by cogrinding with dextrin under defined moisture conditions. Powder Technol 2012;221:213–9. doi:10.1016/j.powtec.2012.01.004.
[151] Kipp JE, Wong JCT, Doty MJ, Rebbeck CL. Microprecipitation Method For Preparing Submicron Suspensions, United States Patent 6,607,784, Baxter International Inc. Deerfield, IL), USA 2003;14.
[152] Rabinow BE. Nanosuspensions in drug delivery. Nat Rev Drug Discov 2004;3:785–96.
[153] Möschwitzer J, Müller RH. New method for the effective production of ultrafine drug nanocrystals. J Nanosci Nanotechnol 2006;6:3145–53.
[154] Shegokar R, Müller RH. Nanocrystals: Industrially feasible multifunctional formulation technology for poorly soluble actives. Int J Pharm 2010;399:129–39. doi:10.1016/j.ijpharm.2010.07.044.
[155] Chan HK, Kwok PCL. Production methods for nanodrug particles using the bottom-up approach. Adv Drug Deliv Rev 2011;63:406–16. doi:10.1016/j.addr.2011.03.011.
[156] Dirksen J a., Ring T a. Fundamentals of crystallization: Kinetic effects on particle size distributions and morphology. Chem Eng Sci 1991;46:2389–427. doi:10.1016/0009-2509(91)80035-W.
[157] Wang X, Li Y. Monodisperse nanocrystals: general synthesis, assembly, and their applications. Chem Commun (Camb) 2007:2901–10. doi:10.1039/b700183e.
[158] Zhang JY, Shen ZG, Zhong J, Hu TT, Chen JF, Ma ZQ, et al. Preparation of amorphous cefuroxime axetil nanoparticles by controlled nanoprecipitation method without surfactants. Int J Pharm 2006;323:153–60. doi:10.1016/j.ijpharm.2006.05.048.
[159] De Waard H, Frijlink HW, Hinrichs WLJ. Bottom-up preparation techniques for nanocrystals of lipophilic drugs. Pharm Res 2011;28:1220–3. doi:10.1007/s11095-010-0323-3.
[160] D. Horn EL. Preparation and characterization of nano-sized carotenoid hydrosols. Fine Part Sci Technol From Micro to Nanoparticles, Kluwer Acad Dordrecht, Netherlands 1995:761–75.
[161] B.K. Johnson RK. Flash nanoprecipitation of organic actives and block copolymers using a confined impinging jets mixer. Aust J Chem 2003;56:1021–4.
[162] Xia D, Quan P, Piao H, Piao H, Sun S, Yin Y, et al. Preparation of stable nitrendipine nanosuspensions using the precipitation-ultrasonication method for enhancement of dissolution and oral bioavailability. Eur J Pharm Sci 2010;40:325–34. doi:10.1016/j.ejps.2010.04.006.
[163] Chen JF, Zhou MY, Shao L, Wang YY, Yun J, Chew NYK, et al. Feasibility of preparing nanodrugs by high-gravity reactive precipitation. Int J Pharm 2004;269:267–74. doi:10.1016/j.ijpharm.2003.09.044.
[164] M. List HS. Hydrosols of pharmacologically active agents and their pharmaceutical compositions comprising them, 1995.
[165] P. Gassmann HS. Improvements in pharmaceutical compositions WO 1992;92/18105.
[166] H. Auweter, H. Bohn, R. Heger, D. Horn, B. Siegel, K. Siemensmeyer. Precipitated water-insoluble colorants in colloid disperse form, 2002.
[167] N. Rasenack BWM. Dissolution rate enhancement byin situ micronization of poorly

water-soluble drugs,. Pharm Res 2002;19:1894–900.
[168] Douroumis D, Fahr A. Enhanced dissolution of Oxcarbazepine microcrystals using a static mixer process. Colloids Surfaces B Biointerfaces 2007;59:208–14.
[169] Douroumis D, Fahr A. Nano-and micro-particulate formulations of poorly water-soluble drugs by using a novel optimized technique. Eur J Pharm Biopharm 2006;63:173–5.
[170] List M, Sucker H. Pharmaceutical colloidal hydrosols for injection, 1988.
[171] R.C. Oppenheim, J.J. Marty, P.P. Speiser. Injectable compositions, nanoparticles useful therein, and process of manufacturing, 1978.
[172] Chow, A.H.L., Chow, P.K.K., Wang, Z., Grant DG. Modification of acetaminophen crystals: influence of growth in aqueous solutions containing p-acetoxyacetanilide on crystal properties. Int J Pharm 1985;24, May:239–58.
[173] Sauter C, Emin M a., Schuchmann HP, Tavman S. Influence of hydrostatic pressure and sound amplitude on the ultrasound induced dispersion and de-agglomeration of nanoparticles. Ultrason Sonochem 2008;15:517–23. doi:10.1016/j.ultsonch.2007.08.010.
[174] Van Eerdenbrugh B, Froyen L, Martens J a., Blaton N, Augustijns P, Brewster M, et al. Characterization of physico-chemical properties and pharmaceutical performance of sucrose co-freeze-dried solid nanoparticulate powders of the anti-HIV agent loviride prepared by media milling. Int J Pharm 2007;338:198–206. doi:10.1016/j.ijpharm.2007.02.005.
[175] Thakur R, Gupta RB. Formation of phenytoin nanoparticles using rapid expansion of supercritical solution with solid cosolvent (RESS-SC) process. Int J Pharm 2006;308:190–9. doi:10.1016/j.ijpharm.2005.11.005.
[176] Moribe K, Fukino M, Tozuka Y, Higashi K, Yamamoto K. Prednisolone multicomponent nanoparticle preparation by aerosol solvent extraction system. Int J Pharm 2009;380:201–5. doi:10.1016/j.ijpharm.2009.06.030.
[177] Zhang J, Huang Y, Liu D, Gao Y, Qian S. Preparation of apigenin nanocrystals using supercritical antisolvent process for dissolution and bioavailability enhancement. Eur J Pharm Sci 2013;48:740–7. doi:10.1016/j.ejps.2012.12.026.
[178] Chattopadhyay P, Gupta RB. Production of Antibiotic Nanoparticles Using Supercritical CO 2 as Antisolvent with Enhanced Mass Transfer. Ind Eng Chem Res 2001;40:3530–9. doi:10.1021/ie010040r.
[179] Young TJ, Mawson S, Johnston KP, Henriksen IB, Pace GW, Mishra AK. Rapid expansion from supercritical to aqueous solution to produce submicron suspensions of water-insoluble drugs. Biotechnol Prog 2000;16:402–7. doi:10.1021/bp000032q.
[180] Lee LY, Wang CH, Smith K a. Supercritical antisolvent production of biodegradable micro- and nanoparticles for controlled delivery of paclitaxel. J Control Release 2008;125:96–106. doi:10.1016/j.jconrel.2007.10.002.
[181] Uchida H, Nishijima M, Sano K, Demoto K, Sakabe J, Shimoyama Y. Production of theophylline nanoparticles using rapid expansion of supercritical solutions with a solid cosolvent (RESS-SC) technique. Elsevier BV 2015. doi:10.1016/j.supflu.2015.05.005.
[182] Chen, J.F., Zhou, X.M., Zheng, C. Ultrafine particle synthesis by high-gravity reactive precipitation., 1995.
[183] Chen J-F, Wang Y-H, Guo F, Wang X-M, Zheng C. Synthesis of Nanoparticles with Novel Technology: High-Gravity Reactive Precipitation. Ind Eng Chem Res 2000;39:948–54. doi:10.1021/ie990549a.
[184] Kipp IJE, Us IL, Chung J, Wong T, Doty MJ, Rebbeck CL. United States Patent

MICROPRECIPITATION METHOD FOR 2006;2.
[185] Müller RH, Gohla S, Keck CM. State of the art of nanocrystals - Special features, production, nanotoxicology aspects and intracellular delivery. Eur J Pharm Biopharm 2011;78:1–9. doi:10.1016/j.ejpb.2011.01.007.
[186] Chan HK, Chew NYK. Novel alternative methods for the delivery of drugs for the treatment of asthma. Adv Drug Deliv Rev 2003;55:793–805. doi:10.1016/S0169-409X(03)00078-4.
[187] Liversidge GG. Drug nanocrystals for improved drug delivery. Proc. CRS Work. Part. Drug Deliv. Syst., Kyoto, Japan, July 1996: 1996.
[188] Merisko-Liversidge E, Liversidge GG. Nanosizing for oral and parenteral drug delivery: A perspective on formulating poorly-water soluble compounds using wet media milling technology. Adv Drug Deliv Rev 2011;63:427–40. doi:10.1016/j.addr.2010.12.007.
[189] Ghosh I, Schenck D, Bose S, Ruegger C. Optimization of formulation and process parameters for the production of nanosuspension by wet media milling technique: Effect of Vitamin e TPGS and nanocrystal particle size on oral absorption. Eur J Pharm Sci 2012;47:718–28. doi:10.1016/j.ejps.2012.08.011.
[190] George M, Ghosh I. Identifying the correlation between drug/stabilizer properties and critical quality attributes (CQAs) of nanosuspension formulation prepared by wet media milling technology. Eur J Pharm Sci 2013;48:142–52. doi:10.1016/j.ejps.2012.10.004.
[191] Nakach M, Authelin J-R, Tadros T, Galet L, Chamayou A. Engineering of nano-crystalline drug suspensions: Employing a physico-chemistry based stabilizer selection methodology or approach. Int J Pharm 2014;476:277–88. doi:10.1016/j.ijpharm.2014.09.048.
[192] Merisko-Liversidge E, Sarpotdar P, Bruno J, Hajj S, Wei L, Peltier N, et al. Formulation and antitumor activity evaluation of nanocrystalline suspensions of poorly soluble anticancer drugs. Pharm Res 1996;13:272–8. doi:10.1023/A:1016051316815.
[193] Bottomley. Nanotechnology for drug delivery: a validated technology. 2006.
[194] Gao L, Liu G, Ma J, Wang X, Zhou L, Li X. Drug nanocrystals: In vivo performances. J Control Release 2012;160:418–30. doi:10.1016/j.jconrel.2012.03.013.
[195] Sigfridsson K, Lundqvist AJ, Strimfors M. Particle size reduction for improvement of oral absorption of the poorly soluble drug UG558 in rats during early development. Drug Dev Ind Pharm 2009;35:1479–86. doi:10.3109/03639040903025855.
[196] Sigfridsson K, Nordmark A, Theilig S, Lindahl A. A formulation comparison between micro- and nanosuspensions: the importance of particle size for absorption of a model compound, following repeated oral administration to rats during early development. Drug Dev Ind Pharm 2011;37:185–92. doi:10.3109/03639045.2010.504209.
[197] Wahlstrom JL, Chiang PC, Ghosh S, Warren CJ, Wene SP, Albin L a., et al. Pharmacokinetic evaluation of a 1,3-dicyclohexylurea nanosuspension formulation to support early efficacy assessment. Nanoscale Res Lett 2007;2:291–6. doi:10.1007/s11671-007-9063-7.
[198] Ali HSM, York P, Ali AM a, Blagden N. Hydrocortisone nanosuspensions for ophthalmic delivery: A comparative study between microfluidic nanoprecipitation and wet milling. J Control Release 2011;149:175–81. doi:10.1016/j.jconrel.2010.10.007.
[199] Sharma P, Denny W a., Garg S. Effect of wet milling process on the solid state of indomethacin and simvastatin. Int J Pharm 2009;380:40–8. doi:10.1016/j.ijpharm.2009.06.029.

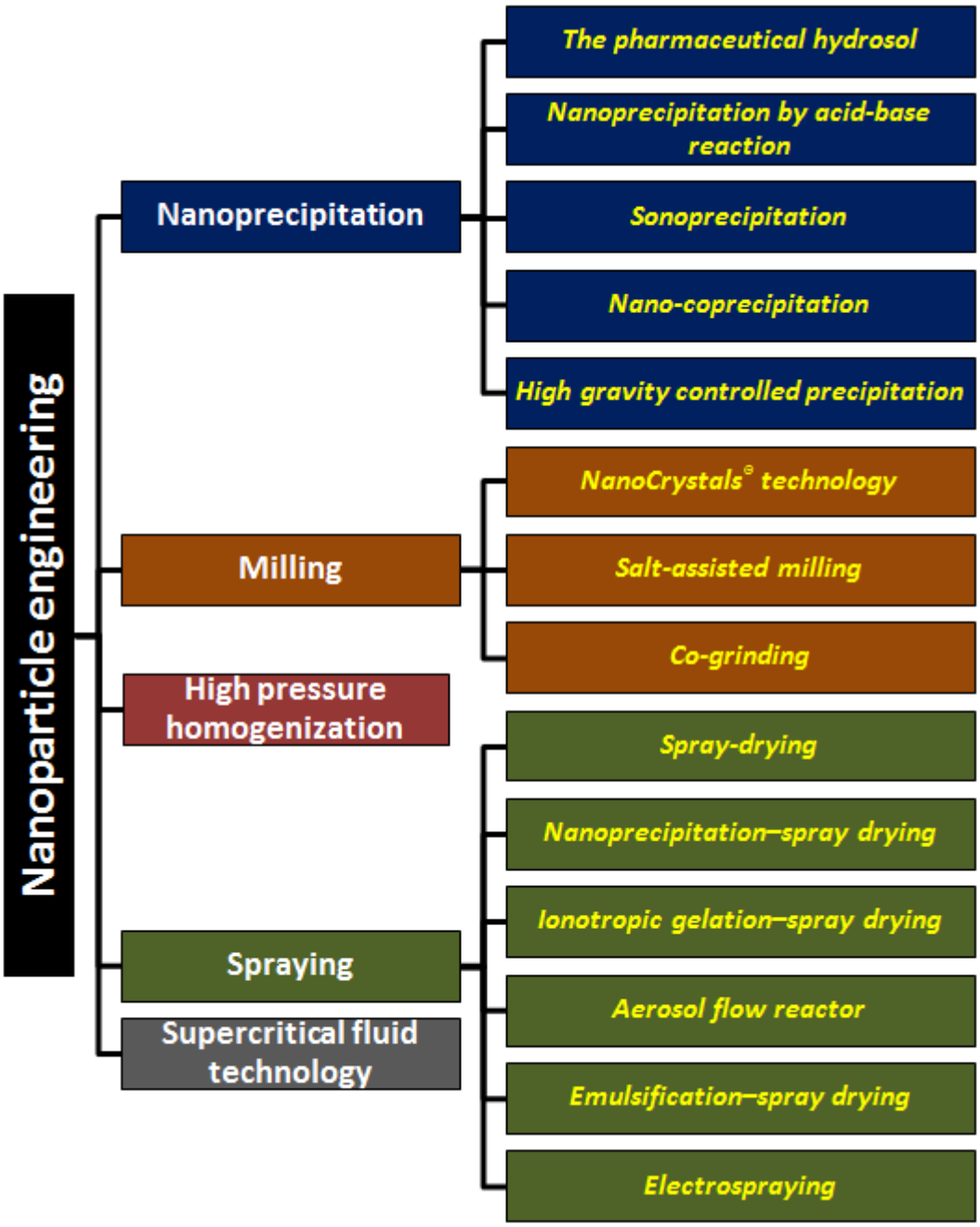
[200] Font J, Muntasell J, Cesari E. Amorphization of organic compounds by ball milling. Mater Res Bull 1997;32:1691–6. doi:10.1016/S0025-5408(97)00162-1.
[201] Willart JF, De Gusseme a., Hemon S, Odou G, Danede F, Descamps M. Direct crystal to glass transformation of trehalose induced by ball milling. Solid State Commun 2001;119:501–5. doi:10.1016/S0038-1098(01)00283-6.
[202] Ward GH, Schultz RK. Process-induced crystallinity changes in albuterol sulfate and its effect on powder physical stability. Pharm Res 1995;12:773–9. doi:10.1023/A:1016232230638.
[203] Hennart SL a, Domingues MC, Wildeboer WJ, van Hee P, Meesters GMH. Study of the process of stirred ball milling of poorly water soluble organic products using factorial design. Powder Technol 2010;198:56–60. doi:10.1016/j.powtec.2009.10.014.
[204] Juhnke M, Berghausen J, Timpe C. Accelerated formulation development for nanomilled active pharmaceutical ingredients using a screening approach. Chem Eng Technol 2010;33:1412–8. doi:10.1002/ceat.201000062.
[205] Li M, Yaragudi N, Afolabi a., Dave R, Bilgili E. Sub-100nm drug particle suspensions prepared via wet milling with low bead contamination through novel process intensification. Chem Eng Sci 2015;130:207–20. doi:10.1016/j.ces.2015.03.020.
[206] Ostrander KD, Bosch HW, Bondanza DM. An in-vitro assessment of a NanoCrystal(TM) beclomethasone dipropionate colloidal dispersion via ultrasonic nebulization. Eur J Pharm Biopharm 1999;48:207–15. doi:10.1016/S0939-6411(99)00049-1.
[207] T.S. Wiedmann, L. DeCastro RWW. Nebulization of NanoCrystals^{TM}: production of a respirable solid-in-liquid-in-air colloidal dispersion. Pharm Res 1997;14:112–6.
[208] Dai WG, Dong LC, Song YQ. Nanosizing of a drug/carrageenan complex to increase solubility and dissolution rate. Int J Pharm 2007;342:201–7. doi:10.1016/j.ijpharm.2007.04.032.
[209] Munoz A, Guichard JP, Reginault PH. Micronised fenofibrate. Atherosclerosis 1994;110:S45–8.
[210] Vogt M, Kunath K, Dressman JB. Dissolution enhancement of fenofibrate by micronization, cogrinding and spray-drying: comparison with commercial preparations. Eur J Pharm Biopharm 2008;68:283–8.
[211] Sugimoto M, Okagaki T, Narisawa S, Koida Y, Nakajima K. Improvement of dissolution characteristics and bioavailability of poorly water-soluble drugs by novel cogrinding method using water-soluble polymer. Int J Pharm 1998;160:11–9. doi:10.1016/S0378-5173(97)00293-7.
[212] KUBo H, MIZOBE M. Improvement of Dissolution Rate and Oral Bioavailability of a Sparingly Water-Soluble Drug,(.+-.)-5-((2-(2 Naphthalenylmethyl)-5-benzoxazolyl)-methyl)-2, 4-thiazolidinedione, in Co-ground Mixture with D-Mannitol. Biol Pharm Bull 1997;20:460–3.
[213] Kipp JE. The role of solid nanoparticle technology in the parenteral delivery of poorly water-soluble drugs. Int J Pharm 2004;284:109–22. doi:10.1016/j.ijpharm.2004.07.019.
[214] Parikh I, Selvaraj U. Composition and method of preparing microparticles of water-insoluble substances 1999.
[215] Muller RH, Becker R, Kruss B, Peters K. Pharmaceutical nanosuspensions for medicament administration as systems with increased saturation solubility and rate of solution 1999.
[216] Haynes DH. Phospholipid-coated microcrystals: injectable formulations of water-

insoluble drugs 1992.
[217] Jafari SM, He Y, Bhandari B. Optimization of nano-emulsions production by microfluidization. Eur Food Res Technol 2007;225:733–41.
[218] Jacobs C, Kayser O, Müller RH. Nanosuspensions as a new approach for the formulation for the poorly soluble drug tarazepide. Int J Pharm 2000;196:161–4. doi:10.1016/S0378-5173(99)00412-3.
[219] Weiss J, Decker E a., McClements DJ, Kristbergsson K, Helgason T, Awad T. Solid lipid nanoparticles as delivery systems for bioactive food components. Food Biophys 2008;3:146–54. doi:10.1007/s11483-008-9065-8.
[220] Müller RH, Radtke M, Wissing S a. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev 2002;54:131–55. doi:10.1016/S0169-409X(02)00118-7.
[221] Keck CM, Müller RH. Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur J Pharm Biopharm 2006;62:3–16. doi:10.1016/j.ejpb.2005.05.009.
[222] Hecq J, Deleers M, Fanara D, Vranckx H, Boulanger P, Le Lamer S, et al. Preparation and in vitro/in vivo evaluation of nano-sized crystals for dissolution rate enhancement of ucb-35440-3, a highly dosed poorly water-soluble weak base. Eur J Pharm Biopharm 2006;64:360–8. doi:10.1016/j.ejpb.2006.05.008.
[223] Dong Y, Feng SS. Poly(d,l-lactide-co-glycolide) (PLGA) nanoparticles prepared by high pressure homogenization for paclitaxel chemotherapy. Int J Pharm 2007;342:208–14. doi:10.1016/j.ijpharm.2007.04.031.
[224] Potta SG, Minemi S, Nukala RK, Peinado C, Lamprou DA, Urquhart A, et al. Preparation and characterization of ibuprofen solid lipid nanoparticles with enhanced solubility. J Microencapsul 2011;28:74–81.
[225] Potta SG, Minemi S, Nukala RK, Peinado C, Lamprou DA, Urquhart A, et al. Development of solid lipid nanoparticles for enhanced solubility of poorly soluble drugs. J Biomed Nanotechnol 2010;6:634–40.
[226] Hu J, Johnston KP, Williams RO. Nanoparticle engineering processes for enhancing the dissolution rates of poorly water soluble drugs. Drug Dev Ind Pharm 2004;30:233–45. doi:10.1081/DDC-120030422.
[227] M.C. Julienne, M.J. Alonso, J.L. G6mez Amoza JPB. Preparation of poly(d,l-lactide/glycollde) nanoparticles of controlled particle size distribution: application of experimental designs. DRUG Dev Ind Pharm 1992;18:1063–77.
[228] Lee WK, Park JY, Yang EH, Suh H, Kim SH, Chung DS, et al. Investigation of the factors influencing the release rates of cyclosporin A-loaded micro- and nanoparticles prepared by high-pressure homogenizer. J Control Release 2002;84:115–23. doi:10.1016/S0168-3659(02)00239-0.
[229] Souto EB, Wissing S a., Barbosa CM, Müller RH. Development of a controlled release formulation based on SLN and NLC for topical clotrimazole delivery. Int J Pharm 2004;278:71–7. doi:10.1016/j.ijpharm.2004.02.032.
[230] Liu J, Hu W, Chen H, Ni Q, Xu H, Yang X. Isotretinoin-loaded solid lipid nanoparticles with skin targeting for topical delivery. Int J Pharm 2007;328:191–5. doi:10.1016/j.ijpharm.2006.08.007.
[231] Müller RH, Mäder K, Gohla S. Solid lipid nanoparticles (SLN) for controlled drug delivery - A review of the state of the art. Eur J Pharm Biopharm 2000;50:161–77.

doi:10.1016/S0939-6411(00)00087-4.
[232] Jacobs C, Müller RH. Production and characterization of a budesonide nanosuspension for pulmonary administration. Pharm Res 2002;19:189–94. doi:10.1023/A:1014276917363.
[233] Silva a. C, González-Mira E, García ML, Egea M a., Fonseca J, Silva R, et al. Preparation, characterization and biocompatibility studies on risperidone-loaded solid lipid nanoparticles (SLN): High pressure homogenization versus ultrasound. Colloids Surfaces B Biointerfaces 2011;86:158–65. doi:10.1016/j.colsurfb.2011.03.035.
[234] Kluge J, Muhrer G, Mazzotti M. High pressure homogenization of pharmaceutical solids. J Supercrit Fluids 2012;66:380–8. doi:10.1016/j.supflu.2012.01.009.
[235] Pilcer G, Vanderbist F, Amighi K. Preparation and characterization of spray-dried tobramycin powders containing nanoparticles for pulmonary delivery. Int J Pharm 2009;365:162–9.
[236] Percy SR. Improvement in drying and concentrating of liquid substances by atomizing., 1872.
[237] K. Cal KS. Spray drying technique. I. Hardware and process parameters. J Pharm Sci 2010;99:575–86.
[238] Heng D, Lee SH, Ng WK, Tan RBH. The nano spray dryer B-90. Expert Opin Drug Deliv 2011;8:965–72. doi:10.1517/17425247.2011.588206.
[239] Li X, Anton N, Arpagaus C, Belleteix F, Vandamme TF. Nanoparticles by spray drying using innovative new technology: The Buchi Nano Spray Dryer B-90. J Control Release 2010;147:304–10. doi:10.1016/j.jconrel.2010.07.113.
[240] SAHOO NG, ABBAS A, JUDEH Z, LI CM, YUEN K-H. Solubility Enhancement of a Poorly Water-Soluble Anti-Malarial Drug: Experimental Design and Use of a Modified Multifluid Nozzle Pilot Spray Drier. Wiley Intersci 2008.
[241] Baldinger A, Clerdent L, Rantanen J, Yang M, Grohganz H. Quality by design approach in the optimization of the spray-drying process. Pharm Dev Technol 2012;17:389–97. doi:10.3109/10837450.2010.550623.
[242] Paudel A, Worku ZA, Meeus J, Guns S, Van Den Mooter G. Manufacturing of solid dispersions of poorly water soluble drugs by spray drying: Formulation and process considerations. Int J Pharm 2013;453:253–84. doi:10.1016/j.ijpharm.2012.07.015.
[243] Corrigan OI. Thermal analysis of spray dried products. Thermochim Acta 1995;248:245–58. doi:10.1016/0040-6031(94)01891-J.
[244] Abdelwahed W, Degobert G, Stainmesse S, Fessi H. Freeze-drying of nanoparticles: Formulation, process and storage considerations. Adv Drug Deliv Rev 2006;58:1688–713. doi:10.1016/j.addr.2006.09.017.
[245] Iskandar F, Gradon L, Okuyama K. Control of the morphology of nanostructured particles prepared by the spray drying of a nanoparticle sol. J Colloid Interface Sci 2003;265:296–303. doi:10.1016/S0021-9797(03)00519-8.
[246] AS M. Handbook of industrial drying. 3rd edition. Boca Raton: CRC Press; 2006.
[247] KRZYSZTOF SOLLOHUB KC. Spray Drying Technique: II. Current Applications in Pharmaceutical Technology. Wiley Intersci 2009.
[248] Schmid K, Arpagaus C, Friess W. Evaluation of the Nano Spray Dryer B-90 for pharmaceutical applications. Pharm Dev Technol 2011;16:287–94. doi:10.3109/10837450.2010.485320.
[249] Sosnik A, Seremeta KP. Advantages and challenges of the spray-drying technology for the production of pure drug particles and drug-loaded polymeric carriers. Adv Colloid

Interface Sci 2015. doi:10.1016/j.cis.2015.05.003.
[250] Nandiyanto ABD, Okuyama K. Progress in developing spray-drying methods for the production of controlled morphology particles: From the nanometer to submicrometer size ranges. Adv Powder Technol 2011;22:1–19. doi:10.1016/j.apt.2010.09.011.
[251] Schafroth N, Arpagaus C, Jadhav UY, Makne S, Douroumis D. Nano and microparticle engineering of water insoluble drugs using a novel spray-drying process. Colloids Surfaces B Biointerfaces 2012;90:8–15. doi:10.1016/j.colsurfb.2011.09.038.
[252] Peltonen L, Valo H, Kolakovic R, Laaksonen T, Hirvonen J. Electrospraying, spray drying and related techniques for production and formulation of drug nanoparticles. Expert Opin Drug Deliv 2010;7:705–19. doi:10.1517/17425241003716802.
[253] Yin SX, Franchini M, Chen J, Hsieh A, Jen S, Lee T, et al. Bioavailability enhancement of a COX-2 inhibitor, BMS-347070, from a nanocrystalline dispersion prepared by spray-drying. J Pharm Sci 2005;94:1598–607. doi:10.1002/jps.20366.
[254] Mizoe T, Ozeki T, Okada H. Preparation of drug nanoparticle-containing microparticles using a 4-fluid nozzle spray drier for oral, pulmonary, and injection dosage forms. J Control Release 2007;122:10–5. doi:10.1016/j.jconrel.2007.06.001.
[255] Calvo P, Remunan-Lopez C. Novel hydrophilic chitosan-polyethylene oxide nanoparticles as protein carriers. J Appl … 1997:125–32. doi:10.1002/(SICI)1097-4628(19970103)63:1<125::AID-APP13>3.0.CO;2-4.
[256] Grenha A, Grainger CI, Dailey LA, Seijo B, Martin GP, Remuñán-López C, et al. Chitosan nanoparticles are compatible with respiratory epithelial cells in vitro. Eur J Pharm Sci 2007;31:73–84. doi:10.1016/j.ejps.2007.02.008.
[257] Eerikäinen H, Kauppinen EI. Preparation of polymeric nanoparticles containing corticosteroid by a novel aerosol flow reactor method. Int J Pharm 2003;263:69–83. doi:10.1016/S0378-5173(03)00370-3.
[258] Eerikäinen H, Watanabe W, Kauppinen EI, Ahonen PP. Aerosol flow reactor method for synthesis of drug nanoparticles. Eur J Pharm Biopharm 2003;55:357–60. doi:10.1016/S0939-6411(03)00005-5.
[259] Eerikäinen H, Kauppinen EI, Kansikas J. Polymeric drug nanoparticles prepared by an aerosol flow reactor method. Pharm Res 2004;21:136–43.
[260] Date A a., Patravale VB. Current strategies for engineering drug nanoparticles. Curr Opin Colloid Interface Sci 2004;9:222–35. doi:10.1016/j.cocis.2004.06.009.
[261] Yamamoto H, Hoshina W, Kurashima H, Takeuchi H, Kawashima Y, Yokoyama T, et al. Engineering of poly(DL-lactic-co-glycolic acid) nanocomposite particles for dry powder inhalation dosage forms of insulin with the spray-fluidized bed granulating system. Adv Powder Technol 2007;18:215–28. doi:10.1163/156855207780208592.
[262] Arya N, Chakraborty S, Dube N, Katti DS. Electrospraying: A facile technique for synthesis of chitosan-based micro/nanospheres for drug delivery applications. J Biomed Mater Res - Part B Appl Biomater 2009;88:17–31. doi:10.1002/jbm.b.31085.
[263] Loscertales IG, Barrero a, Guerrero I, Cortijo R, Marquez M, Gañán-Calvo a M. Micro/nano encapsulation via electrified coaxial liquid jets. Science 2002;295:1695–8. doi:10.1126/science.1067595.
[264] Park CG, Kim E, Park M, Park JH, Choy Y Bin. A nanofibrous sheet-based system for linear delivery of nifedipine. J Control Release 2011;149:250–7. doi:10.1016/j.jconrel.2010.10.023.
[265] Ho H, Lee J. Redispersible drug nanoparticles prepared without dispersant by electro-

spray drying. Drug Dev Ind Pharm 2012;38:744–51. doi:10.3109/03639045.2011.624522.
[266] York P. Strategies for particle design using supercritical fluid technologies. Pharm Sci Technol Today 1999;2:430–40. doi:10.1016/S1461-5347(99)00209-6.
[267] Türk M, Hils P, Helfgen B, Schaber K, Martin H-J, Wahl MA. Micronization of pharmaceutical substances by the rapid expansion of supercritical solutions (RESS): a promising method to improve bioavailability of poorly soluble pharmaceutical agents. J Supercrit Fluids 2002;22:75–84.
[268] Campardelli R, Baldino L, Reverchon E. Supercritical fluids applications in nanomedicine. J Supercrit Fluids 2015;101:193–214. doi:10.1016/j.supflu.2015.01.030.
[269] Türk M, Bolten D. Formation of submicron poorly water-soluble drugs by rapid expansion of supercritical solution (RESS): Results for Naproxen. J Supercrit Fluids 2010;55:778–85. doi:10.1016/j.supflu.2010.09.023.
[270] Jung J, Perrut M. Particle design using supercritical fluids: Literature and patent survey. J Supercrit Fluids 2001;20:179–219. doi:10.1016/S0896-8446(01)00064-X.
[271] Esfandiari N. Production of micro and nano particles of pharmaceutical by supercritical carbon dioxide. J Supercrit Fluids 2015;100:129–41. doi:10.1016/j.supflu.2014.12.028.
[272] Kalantarian P, Haririan I, Najafabadi AR, Shokrgozar MA, Vatanara A. Entrapment of 5-fluorouracil into PLGA matrices using supercritical antisolvent processes. J Pharm Pharmacol 2011;63:500–6. doi:10.1111/j.2042-7158.2010.01249.x.
[273] Byrappa K, Ohara S, Adschiri T. Nanoparticles synthesis using supercritical fluid technology - towards biomedical applications. Adv Drug Deliv Rev 2008;60:299–327. doi:10.1016/j.addr.2007.09.001.
[274] Bahrami M, Ranjbarian S. Production of micro- and nano-composite particles by supercritical carbon dioxide. J Supercrit Fluids 2007;40:263–83. doi:10.1016/j.supflu.2006.05.006.
[275] Perrut M, Jung J, Leboeuf F. Enhancement of dissolution rate of poorly-soluble active ingredients by supercritical fluid processes: Part I: Micronization of neat particles. Int J Pharm 2005;288:3–10. doi:10.1016/j.ijpharm.2004.09.007.
[276] Muhammad SAFAS, Langrish T, Tang P, Adi H, Chan HK, Kazarian SG, et al. A novel method for the production of crystalline micronised particles. Int J Pharm 2010;388:114–22. doi:10.1016/j.ijpharm.2009.12.047.
[277] Alexandridis P, Alan Hatton T. Poly(ethylene oxide)□poly(propylene oxide)□poly(ethylene oxide) block copolymer surfactants in aqueous solutions and at interfaces: thermodynamics, structure, dynamics, and modeling. Colloids Surfaces A Physicochem Eng Asp 1995;96:1–46. doi:10.1016/0927-7757(94)03028-X.
[278] Finlay WH, Stapleton KW, Zuberbuhler P. Fine particle fraction as a measure of mass depositing in the lung during inhalation of nearly isotonic nebulized aerosols. J Aerosol Sci 1997;28:1301–9.
[279] Finlay WH, Gehmlich MG. Inertial sizing of aerosol inhaled from two dry powder inhalers with realistic breath patterns versus constant flow rates. Int J Pharm 2000;210:83–95.
[280] Shi YL, Asefa T. Tailored core - Shell - Shell nanostructures: Sandwiching gold nanoparticles between silica cores and tunable silica shells. Langmuir 2007;23:9455–62. doi:10.1021/la700863g.
[281] Card JW, Zeldin DC, Bonner JC, Nestmann ER. Pulmonary applications and toxicity of engineered nanoparticles. Am J Physiol Cell Mol Physiol 2008;295:L400–11.



Graphical abstract

Highlights

- Nanoparticle engineering is a promising tool to resolve many current issues associated with poorly soluble APIs such as those related to poor solubility and dissolution rate.
- Serious potential challenges are associated with the preparation of nanosized APIs such as separating nanosized APIs from surfactants, low formulation yield, contamination with microsized particles, and those related to the ability to re-suspend nanosized APIs after drying.

The optimization of nanosizing processes using quality-by-design methods might open new horizons in the development of pharmaceutical formulations.